CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Prothioconazole

Chemical Code # 6005, **Tolerance #** 53088
SB 950 # NA

6/28/10

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect*
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect**
Reproduction, rat:	No data gap, possible adverse effect***
Teratology, rat:	No data gap, possible adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	No data gap, no adverse effect

Toxicology one-liners are attached.

All record numbers through #247430 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: S100615
Revised by T. Moore, 6/28/10

*: Non-oncogenic effect was noted in the rat oncogenicity study.
**: Non-oncogenic effect.
***: Non-reproductive or developmental effect.

Note: The test material SXX 0665 is the desthio-analogue of prothioconazole. It was originally proposed for use as an active ingredient and is a significant metabolite of prothioconazole.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

Study not submitted.

CHRONIC TOXICITY, RAT

** 53088-0129; 247354; "JAU 6476: Study on Chronic Toxicity in Wistar Rats, Administration via Gavage over 1 Year"; (U. Wirnitzer, A. Popp; Bayer AG, Department of Toxicology, 42096 Wuppertal, Germany; Report No. 30536; 12/14/00); Twenty Wistar rats/sex/group were dosed orally by gavage with 0, 5, 50 or 750 mg/kg/day of JAU 6476 (prothioconazole technical) (batch no. 06233/0044; purity: 98.8 - 99.4%) for one year. One male each died in the control, 5 and 50 mg/kg groups and 3 males died in the 750 mg/kg group. One female and two females in the 50 and 750 mg/kg groups, respectively, died. The mean body weights of both sexes in the 750 mg/kg group were less than those of the control group throughout much of the treatment period ($p<0.05$ or 0.01). The mean water uptake of both sexes in the 750 mg/kg group was greater than that of the control group throughout the study ($p<0.01$). The food consumption was not apparently affected by the treatment. No treatment-related effect was noted in the hematology or the functional observational battery. In the clinical chemistry evaluation, the mean serum creatinine, urea and bilirubin levels for both sexes in the 750 mg/kg group were greater than the control values at various time points throughout the study ($p<0.05$ or 0.01). The T4 serum levels for both sexes in the 750 mg/kg group were less than the control values at all of the time points assayed (NS, $p<0.05$ or 0.01). In the urinalysis, the mean urine volumes were increased for both sexes in the 750 mg/kg group during the study (NS, $p<0.05$ or 0.01). The density and pH of the urine were generally less for these same animals (NS, $p<0.05$ or 0.01). The mean relative liver and kidney weights of both sexes in the 750 mg/kg group were greater than those of the controls (NS, $p<0.01$). The mean relative adrenal and testes weights of the 750 mg/kg males were greater than the control values ($p<0.01$). In the histopathological evaluation, the cytoplasmic changes were noted in the livers of both sexes in the 750 mg/kg group. Chronic progressive nephropathy was increasingly severe in the kidneys of both sexes in the 750 mg/kg group. **No adverse effect was evident. Rat Chronic Oral Toxicity NOEL:** (M/F) 50 mg/kg/day (based upon the lesions in the livers and kidneys and effects on clinical chemistry parameters-related to kidney function in the 750 mg/kg treatment group); **Study acceptable.** (Moore, 3/18/10)

CHRONIC TOXICITY, DOG

**** 53088-0130; 247363**; "Technical Grade JAU 6476: A Chronic Oral Gavage Study in the Beagle Dog"; (R.D. Jones, B.P. Stuart; Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS; Report No. 110921; 12/7/01); Four beagle dogs/sex/group were dosed orally by gavage with 0, 5, 40 or 125 mg/kg/day of JAU 6476 (Prothioconazole technical) (batch no. 6233/0031; purity: 98.8% (7/99), 98.6% (4/00), 98.6% (8/00), 98.4% (2/01)), 5 days/week for one year. No deaths resulted from the treatment. The body weight gain and food consumption of the females in the 125 mg/kg group was less than that of the control group over the course of the study. Clinical signs, ECG, neurological, and ophthalmological data did not reveal any treatment-related effects. No treatment-related effects were evident in the hematology, clinical chemistry or urinalysis. The mean relative liver weights of both sexes and the relative kidney weight of the females in the 125 mg/kg group were less than the control values ($p<0.05$). In the histopathology, all four of the females and one male in the 125 mg/kg group demonstrated chronic inflammation in the kidneys. Pigmentation was noted in the kidneys, liver and spleen of dogs in both 40 and 125 mg/kg groups. No physiological relevance was apparent for this observation. **Possible adverse effect:** chronic renal inflammation; **Dog Chronic Oral Toxicity NOEL:** (M/F) 40 mg/kg/day (based upon increased relative liver weights in both sexes and the increased relative kidney weights and incidence of chronic renal inflammation of the females in the 125 mg/kg group); **Study acceptable.** (Moore, 3/22/10)

ONCOGENICITY, RAT

**** 53088-0132; 247365**; "JAU 6476: Study on Carcinogenicity in Wistar Rats (Administration by Gavage over 2 Years)"; (U. Wirnitzer, E. Hartmann; Bayer AG, PH-PD Toxicology, Cancerogenicity and Genotoxicity, 42096 Wuppertal, Germany; Report No. 31512; 11/16/01); Fifty Wistar rats/sex/group were dosed orally by gavage with 0, 5, 50 or 750 mg/kg/day of JAU 6476 (prothioconazole technical) (batch no. 06233/0044; purity: 98.5 to 99.1%) for 2 years. The treatment level for the high dose group was adjusted to 500 mg/kg/day for the males in study week 84 and to 625 mg/kg/day for the females in study week 56 due to the poor general condition of the animals in this group. Only 26% of the males in the high dose group survived to the termination of the study. The mean body weights of both sexes in the high dose group were less than the control values throughout the study ($p<0.01$). In contrast, the food consumption (g/animal/day) and water intake of both sexes in the high dose group were significantly greater than the control group's values throughout the study. In the hematology, the mean red blood cell count, hemoglobin concentration and hematocrit of both sexes in the high dose group were less than those of the control group throughout the 2nd year of the study. The males were affected to a greater degree. In the clinical chemistry, urea and creatinine levels were elevated in the serum of the high dose males ($p<0.01$). The total serum protein and albumin concentrations were lower for the high dose males toward the end of the study ($p<0.05$ or 0.01). The T4 level in the serum of both sexes in the high dose group was less than that of the control group throughout the study (NS, $p<0.01$). In the urinalysis, the urine volume excreted by both sexes in the high dose group was greater than the volume excreted by the control group throughout the 2nd year of the study ($p<0.05$ or 0.01). The pH and urine density were less for the males in the high dose group in comparison to the control group ($p<0.05$ or 0.01). Although the density and pH of the urine from the high dose females were less than the control group's values, these parameters were less affected for the females. In the necropsy examination, the mean relative liver and kidney weights of both sexes in the high dose group and the mean absolute liver weight of the females in the high dose group were greater than the control values ($p<0.05$ or 0.01). In the histopathology, hypertrophy was noted in the livers of both sexes in the high dose group and in the 50 ppm males. Eosinophils and clear cell foci were also noted in the livers of both sexes in the high dose group. The incidence of chronic progressive nephropathy in the kidneys was more severe in both sexes of the high dose group than in the control group. Transitional cell hyperplasia was noted in the urinary bladder of both sexes in the high dose group. Tubular atrophy in the testes, atrophy of the prostate, and aspermia/oligospermia in the epididymides was suffered by the high dose males. An increased incidence of diffuse hyperplasia was evident in the parathyroid glands of the high dose males. **Possible adverse effect:** chronic progressive nephropathy. **Rat Chronic Oral Toxicity NOEL:** (M) 5 mg/kg/day (based on the hypertrophy of the liver in the 50 mg/kg/day treatment group); (F) 50 mg/kg/day (based on the liver and kidney lesions noted for the 750/625 mg/kg/day treatment group); **Oncogenicity was not evident. Study acceptable.** (Moore, 3/26/10)

ONCOGENICITY, MOUSE

**** 53088-0133; 247366**; "JAU 6476: Oncogenicity Study in CD-1 Mice (Administration by Gavage for 18 Months)"; (L. Schladt; Bayer AG, PH-PD Toxicology, Rodent Studies and Genotoxicology, 42096 Wuppertal, Germany; Report No. 31510; 11/15/01); Sixty CD-1 mice/sex/group were dosed orally by gavage with 0, 10, 70 or 500 mg/kg/day of JAU 6476 (prothioconazole technical) (batch no. FL.6233/0031, purity: 98.8% (6/3/98), 98.5% (11/25/98), 98.2% (5/21/99), 98.8% (11/19/99), 98.6% (4/28/00)) for 18 months. There was no apparent treatment-related effect upon the survival of the study animals. The mean body weights of both sexes in the 70 and 500 mg/kg groups were less than the control values throughout much of the study ($p<0.05$ or 0.01). The mean food consumption was reduced slightly in a dose-related manner over the course of the study. However, the consumption based on grams/kg of body weight was not affected by the treatment. Although several parameters of the differential white cell count were significantly different between the 500 mg/kg and the control groups, no toxicological significance was apparent. In the necropsy, the mean absolute and relative liver weights of both sexes in the 500 mg/kg group and the males in the 70 mg/kg group and the mean relative liver weight of the 70 mg/kg females were greater than the control values ($p<0.01$). The mean absolute and relative

kidney weights of the 500 mg/kg males and the mean absolute kidney weight of the 500 mg/kg females were less than the control values (p<0.01). In the histopathology, hypertrophy/cytoplasmic changes were noted in the livers of both sexes in the 500 mg/kg group and in the 70 mg/kg males (p<0.01). An increased incidence of tubular degeneration/regeneration was evident in the kidneys of the 70 and 500 mg/kg males and the 500 mg/kg females (p<0.05 or 0.01). Subcapsular degeneration and fibrosis was also evident in the kidneys of both sexes in the 500 mg/kg group (p<0.01). **No oncogenicity was evident. Possible adverse effect** (non carcinogenic endpoint): subcapsular degeneration and fibrosis in the kidneys; **Mouse Chronic Oral Toxicity NOEL:** (M/F) 10 mg/kg/day (based upon lesions in the livers and kidneys of the 70 mg/kg males and the lower mean body weights of the 70 mg/kg females). **Study acceptable.** (Moore, 4/1/10)

REPRODUCTION, RAT

**** 53088-0125; 247350**; "A Two-Generation Reproductive Toxicity with JAU 6476 in the Wistar Rat"; (A.D. Young; Bayer Corporation, Agricultural Division, Toxicology, Stilwell, KS; Report No. 110500; 12/4/01); Thirty Wistar rats/sex/group in the F0 generation were dosed orally by gavage with 0, 10, 100, or 750 mg/kg/day of JAU 6476 technical; batch no. 6233/0031; purity: 98.4% (2/99) for a 10-week premating period, up to a 2-week mating period and 3 weeks both for the gestation and lactation periods. At that time, 30 F1 animals/sex/group were selected as parents and treated for an additional 10 weeks, followed by mating and 3 weeks each for gestation and lactation of the F2 generation. The mean body weights of the 750 mg/kg males in both generations and the 100 mg/kg males in the F1 generation were less than the control values throughout the premating period (p<0.05 or 0.01). Mean food consumption was not affected by the treatment. In the necropsy evaluation, the mean absolute and relative liver weights of both sexes of the 750 mg/kg group in both generations were greater than the control values (NS, p<0.05). The mean absolute and relative liver weights of the F0 males in the 100 mg/kg group were also greater the those of the control group (p<0.05). The mean relative kidney weights of the 750 mg/kg males in both generations were greater than the control values (p<0.05). The mean absolute and relative thymus weights of both sexes in both generations of the 750 mg/kg group and the 100 mg/kg females in the F0 generation were less than the control values (NS, p<0.05). The mean relative seminal vesicle weights of the 100 and 750 mg/kg males in both generations were greater than those of the control group (p<0.05). The mean relative prostate weight of the 750 mg/kg males in the F1 generation was greater than the control value (p<0.05). In the histopathology examination, hepatocytomegaly was noted in the livers of both sexes in the 750 mg/kg and in the 100 mg/kg males in both generations. Nephrosis was evident in the kidneys of both sexes in the 750 mg/kg group in both generations. Among the mating parameters evaluated, the estrous cycle was prolonged for the 750 mg/kg females in both generations (p<0.05). There was a reduced number of implantations per dam for the 750 mg/kg females in both generations. The fertility and gestation indices were not affected by the treatment. The mean pup body weights of the 750 mg/kg groups in both generations were less than those of the control animals during the lactation period (NS, p<0.05 or 0.01). The mean absolute and relative spleen weights of the 750 mg/kg pups in both generations were less than the control group values (p<0.05 or 0.01). Preputial separation was delayed in the male F1 pups of the 750 mg/kg group (p<0.01). The anogenital distance in the F2 offspring was greater for the both sexes in the 750 mg/kg group and for the males in the 100 mg/kg group (p<0.05 or 0.01). This effect was attributed to the larger size of the offspring in this group. No treatment-related effect was noted for the time to vaginal opening and ovarian follicle counts of the F1 female offspring or on spermatogenesis in the adult males of both generations. **Possible adverse effect:** renal nephrosis (non-reproductive or developmental effect); **Parental NOEL:** 10 mg/kg/day (based upon lower mean body weights for the adult F1 males, increased liver weights of the adult F0 males and the hepatocytomegaly in the livers of the males of the F0 generation and the males and females of the F1 generation in the 100 mg/kg treatment group; **Reproductive NOEL:** 100 mg/kg/day (based upon the reduced number of implantations per dam and smaller litter sizes for both generations in the 750 mg/kg group); **Developmental NOEL:** 100 mg/kg/day (based upon lower mean pup weights of both generations during the lactation period and the lower mean

spleen weights of the weanlings in the 750 mg/kg group of both generations); **Study acceptable.** (Moore, 3/10/10)

53088-0128; 247353; "A Pilot Reproductive Toxicity with JAU 6476 Technical in the Wistar Rat"; (A. B. Astroff, K.J. Freshwater; Bayer Corporation, Agricultural Division, Toxicology, Stilwell, KS; Report No. 109079; 10/18/99); Ten Wistar rats/sex/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% (w/v) methylcellulose, 0.4% (v/v) Tween 80 (MCT)), 10, 100, 250 or 500 mg/kg/day for a 4-week premating period, a mating period and 3 weeks both for the gestation and lactation periods. No parental deaths occurred during the study. No treatment-related effects were evident on the mean body weights or food consumption of the parental generation. No treatment-related effect was noted for the fertility or gestation indices. Pup viability was not affected by the treatment. The mean body weights of the offspring in the 500 mg/kg group were less than that of the control group over the course of the lactation period (NS). **No adverse effect indicated. Parental NOEL:** 500 mg/kg/day (based upon the lack of treatment-related effects in the 500 mg/kg group); **Reproductive NOEL:** 500 mg/kg/day (based upon the lack of treatment-related effects in the 500 mg/kg group); **Developmental NOEL:** 500 mg/kg/day (based upon the lack of treatment-related effects in the 500 mg/kg group); **Study supplemental.** (Moore, 3/4/10)

TERATOLOGY, RAT

Oral Route

**** 53088-0109; 247333**; "JAU 6476: Developmental Toxicity Study in Rats after Oral Administration"; (B. Stahl; Bayer AG, Institute for Toxicology, D-42096 Wuppertal, Germany; Report No. 25827; 12/16/96); Twenty six mated female Wistar rats/group were treated orally by gavage with 0 (aqueous 0.5% carboxymethyl cellulose), 80, 500 or 1000 mg/kg/day of JAU 6476 (Prothioconazole technical) (batch no. NLL 6096-4; purity: 99.5%) from day 6 through day 19 of gestation. The mean body weight gain and food consumption of the 1000 mg/kg group dams were less than the control values during the first few days of treatment. Thereafter an effect was not evident. The adjusted mean body weight gain (subtraction of the uterine weight) of the 500 and 1000 mg/kg dams was less than that of the control group over the course of the treatment ($p<0.05$ or 0.01). Alkaline phosphate activity was slightly elevated in the plasma of the 1000 mg/kg dams. The T4 levels were reduced in the plasma of the 500 and 1000 mg/kg dams ($p<0.05$ or 0.01). The relative liver weights of the 1000 mg/kg dams was greater than the control value ($p<0.01$). No treatment-related lesions were noted in the histopathological evaluation of the liver, thyroid or adrenals of the dams. There was a lower mean fetal weight in the 1000 mg/kg group ($p<0.01$). The incidence of microophthalmia was noted litters of all of the treatment groups (0: 0/26 vs. 80: 4/26, 500: 3/22, 1000: 8/24). **Possible adverse effect indicated:** microophthalmia; **Maternal NOEL:** 80 mg/kg/day (based upon treatment-related effects on the water consumption of the 500 mg/kg dams); Developmental NOEL: <80 mg/kg/day (based upon the incidence of microophalmia in the fetuses of the 80 mg/kg treatment group); **Study acceptable.** (1/27/10)

** 53088-0120; 247345; "Technical Grade JAU 6476: A Supplementary PreNatal Developmental Toxicity Study in the Wistar Hanover (Crl:WI(HAN) Rat to Investigate Ocular Abnormalities and Supernumerary Ribs"; (A.D. Young; Bayer CropScience LP, Toxicology, Stilwell, KS; Report No. 201037; 5/10/04); Twenty five mated female Wistar rats/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% carboxymethyl cellulose), 20, 80, or 750 mg/kg/day of Technical grade JAU 6476 (batch no. 6233/0031; purity: 98.7% (9/3/03), 97.8% (5/5/04)) from day 6 through day 19 of gestation. No maternal deaths resulted from the treatment. The mean body weights of the dams were not affected over the course of the treatment. The mean food consumption of the 750 mg/kg dams was less than that of the control group up through day 12. The mean water intake of the 750 mg/kg dams was greater than that of the control group throughout the treatment period. The number of the fetuses with rudimentary ribs in the 750 mg/kg group was greater than that of the control group ($p<0.05$) (no. of litters affected, 0: 11/21 vs. 750: 16/23, no. of fetuses, 0: 26/221 vs. 750: 51/241). There were no treatment-related effects upon the eyes of treated fetuses. **No adverse effect indicated. Maternal NOEL:** 80 mg/kg/day (based upon the treatment-related effect noted on the food consumption and water intake of the 750 mg/kg dams); **Developmental**

NOEL: 80 mg/kg/day (based upon the increased incidence of rudimentary ribs for the fetuses in the 750 mg/kg group); **Study acceptable.** (Moore, 2/23/10)

Dermal Route

** 53088-0116; 247340; "A Dermal Developmental Toxicity Study with (JAU 6476, Technical Material and Products) in the Wistar Rats"; (A.D. Young; Bayer Corporation, Agricultural Division, Toxicology, Stilwell, KS; Report No. 108993; 11/30/01); The skin of 30 or 29 mated Wistar female rats/group was exposed to 0, 62.5, 250 or 1000 mg/kg/day of JAU 6476 (batch no. 6233/0031; purity: 98.9%) or JAU 6476 EC250 (batch no. 06025/0003; a.i.: 25%) for 6 hours/day, from day 6 through day 19 of gestation. (Note: JAU 6476 EC250 undiluted and a 1:3 dilution of this material in deionized water were applied to the skin of the 250 and 62.5 mg/kg groups, respectively). No deaths resulted from this treatment. There were no treatment-related effects upon the mean body weight gain and food consumption of the dams. Dermal irritation was noted at the site of application in the 250 mg/kg group. There was no treatment-related effect upon the development of the fetuses. **No adverse effect indicated. Maternal NOEL:** 1000 mg/kg/day (based upon the lack of a systemic treatment-related effect on the 1000 mg/kg dams); **Developmental NOEL:** 1000 mg/kg/day (based upon the lack of a treatment-related effect on the 1000 mg/kg fetuses); **Study acceptable.** (Moore, 2/17/10)

TERATOLOGY, RABBIT

** 53088-0122; 247347; "Developmental Toxicity Study with JAU 6476: in the Rabbit"; (H. Becker, K. Biedermann; RCC, Research and Consulting Company AG, P.O. Box 4452, Itingen, Switzerland; Project No. 650981; 7/16/98); Twenty four mated Chbb:CH female rabbits/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% sodium carboxymethylcellulose), 10, 30, or 80 mg//kg/day of JAU 6476 technical (batch no. NLL 6096-12; purity: 99.5 to 99.7%) from day 6 through day 27 of gestation. Another treatment group of 24 mated animals, which received 350 mg/kg/day of the test material, was added to the study because no treatment-related effects were evident for the does in the 80 mg/kg group. Also 6 and 7 mated does were added to the 10 and 80 mg/kg treatment groups, respectively, due to an inadequate number of pregnant animals initially in these treatment groups. One doe in the 350 mg/kg group was found dead on day 25 of gestation. The mean body weight gain and food consumption of the 350 mg/kg does were less than the control values throughout much of the treatment period ($p<0.05$ or 0.01). The mean fetal weight of the 350 mg/kg group was less than the control value. Otherwise, no treatment-related effect on fetal development was noted. **No adverse effect indicated. Maternal NOEL:** 80 mg/kg/day (based upon the lower body weight gain and food consumption of the 350 mg/kg does); **Developmental NOEL:** 80 mg/kg/day (based upon the lower mean fetal weights of the 350 mg/kg group); **Study acceptable.** (Moore, 2/25/10)

53088-0124; 247349; "Dose Toleration Study to a Developmental Toxicity Study with JAU 6476 in the Rabbit"; (H. Becker, K. Biedermann; RCC, Research and Consulting Company Ltd. and RCC Umwelchemie AG, CH 4452 Itingen, Switzerland; Project No. 650970; 11/11/97); Three mated female Chinchilla rabbits/group (unless otherwise noted) were dosed orally by gavage with 80, 100, 300, or 480 (5 animals) mg/kg/day of JAU 6476 (Prothioconazole technical) (batch no. NLL 6096-12; purity: 99.7%) from gestation day 6 through 27. Two does in the 480 mg/kg group and one doe each in the 80, 100 and 300 mg/kg groups died during the treatment period. The mean body weight gain of the does in the 300 and 480 mg/kg groups was less than that of the does in the 80 mg/kg group. There was no apparent treatment-related effect on food consumption. The mean fetal weight of the 480 mg/kg group was less than that of the other groups. Nine of the 16 fetuses in that group were less than 19 g in weight. Study data were insufficient to determine if an adverse effect was present or to establish a NOEL. **Study supplemental.** (Moore, 3/1/10**)**

GENE MUTATION

** 53088-0136; 247370; "JAU 6476: *Salmonella*/Microsome Test, Plate Incorporation and Preincubation Method"; (B. Herbold; Bayer AG, Department of Toxicology, 42096 Wuppertal, Germany; Report No. 109055; 2/15/96); *S. typhimurium* TA98, TA100, TA102, TA1535 and

TA1537 strains were incubated with JAU 6476 (prothioconazole technical) (batch no. NLL 6096-4; purity: 99.5%) at levels ranging from 16 to 5000 µg/plate in the first trial and from 1.6 to 500 ug/plate in the second trial under conditions of (-/+) activation for 48 hours at 37° C by means of the plate incorporation method. In the 2nd trial, the bacterial strains were preincubated with the test material for 20 minutes prior to incorporation into the agar. Each treatment was incubated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no apparent treatment-related increase in the incidence of reverse mutation under conditions of non-activation or activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/12/10)

** 53088-0147; 247381; "JAU 6476: Mutagenicity Study for the Detection of Induced Forward Mutations in the V79-HPRT Assay *In Vitro*"; (S. Brendler-Schwaab; Bayer AG, Department of Toxicology, 42096 Wuppertal, Germany; Report No. 109056; 11/4/96); Chinese hamster V79 cells were exposed to JAU 6476 (prothioconazole technical) (batch no. NLL 6096-9.1; purity: 99.8% (11/17/95)) at concentrations ranging from 75 to 200 ug/ml for 5 hours at 37° C with activation. Two trials were performed with duplicate cultures for each treatment level. For the non-activated cultures, the concentrations ranged from 25 to 175 ug/ml in the first trial and from 5 to 150 ug/ml in the second trial. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. No treatment-related increase in forward mutation was evident in the cultures with or w/o activation. **No adverse effect indicated**. The positive controls were functional. **Study acceptable.** (Moore, 4/19/10)

CHROMOSOME EFFECTS

**** 53088-0149; 247383**; "JAU 6476:*In Vitro* Mammalian Chromosome Aberration Test with Chinese Hamster V79 Cells"; (B. Herbold; Bayer AG, Department of Toxicology, 42096 Wuppertal, Germany; Report No. 109057; 12/3/96); Chinese hamster V79 cells were exposed to JAU 6476 (batch no. NLL6096-9.1; purity: 99.8%) for 4 hours at 37° C under conditions of (+/-) activation. In Study No. T 9053704, cells were exposed to concentrations of the test material ranging from 25 to 150 ug/ml and harvested after 18 hours of total incubation time or to concentrations ranging from 75 to 150 ug/ml and harvested after 30 hours of total incubation time. Duplicate cultures were incubated for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used for activation. In Study No. T 5053782, cells were exposed to concentrations of the test material ranging from 50 to 100 ug/ml for 4 hours and harvested after a total of 18 hours of incubation under conditions of nonactivation. A cytotoxicity assay was performed in which cells were exposed to a concentration range of 75 to 150 ug/ml under conditions of (+/-) activation for 4 hours and harvested after a total of 8 hours of incubation. Increased clastogenicity was evident at 75 ug/ml and above in the non-activated assay and at 150 ug/ml in the activated samples (Study No. T 9053704). This effect was noted at 50 ug/ml in the second study under conditions of non-activation. In the cytotoxicity study, the mitotic index was reduced to less than 20% of the control group at the lowest concentration used (75 ug/ml) under conditions of non-activation after a total of 8 hours of incubation. This effect was less apparent for the activated samples. After a total of 18 hours of incubation, the mitotic index was not affected. The author of the report surmised that the delayed cell cycling was a factor in the clastogenicity of the test material. The positive controls were functional. **Possible adverse effect**: clastogenicity. **Study acceptable**. (Moore, 4/22/10)

DNA DAMAGE

** 53088-0152; 247386; "JAU 6476: Micronucleus Test on the Mouse"; (B. Herbold; Bayer AG, Department of Toxicology, 42096 Wuppertal, Germany; Report No. 109058; 10/25/96); Five Hsd/Win mice/sex/time point were dosed by ip injection with 250 mg/kg of JAU 6476 (prothioconazole technical)(batch no. NLL 6096-9.1; purity: 99.9%) and euthanized 16, 24 and 48 hours after dosing. An additional 5 animals/sex/group were treated as negative or positive controls (cyclophosphamide, 20 mg/kg) and euthanized 24 hours after dosing. Bone marrow samples from the femur were examined and the numbers of micronuclei per 1000 polychromatic erythrocytes (PCE) and 1000 normochromatic erythrocytes (NCE) were determined. In addition, the number of NCE/1000 PCE was also recorded. No increase in the number of micronuclei per

1000 PCE's was noted for the treated animals. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 4/29/10)

** 53088-0154; 247388; "JAU 6476: Micronucleus-Test on the Male Mouse"; (B. Herbold; Bayer Healthcare, Health Care Toxicology, 42096 Wuppertal, Germany; Report No. T 5072907; 8/1/03); Five Hsd/Win male mice received two intraperitoneal (ip) injections with 0 (0.5% aqueous Cremophor), 50, 100 or 200 mg/kg of JAU 6476 (batch no. 6023/0016; purity: 95.7%;) 24 hours apart and were euthanized at 24 hours post-final dose. Five males received a single dose of 20 mg/kg of cyclophosphamide and were euthanized at 24 hours post-dose. The femoral bone marrow was harvested and evaluated for the presence of micronuclei in both polychromatic (PCE) and normochromatic erythrocytes (NCE). The number of NCE per 2000 PCE were evaluated per animal as well. Treatment-related signs included apathy, roughened fur, spasm, sternal recumbancy, twitching, periodically stretching of body and difficulty breathing. There was no treatment-related increase in the number of micronuclei per 2000 PCE. The positive control was functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/29/10)

** 53088-0155; 247389; "JAU 6476: Test on Unscheduled DNA Synthesis in Rat Liver Primary Cell Cultures *In Vitro*"; (S. Brendler-Schwaab; Bayer AG, Department of Toxicology, D-42096 Wuppertal, Germany; Report No. 109059; 4/20/98); Primary rat hepatocyte cultures were exposed to JAU 6476 (batch no. NLL 6096-12; purity: 99.7%) at concentrations ranging from 1.0 to 40 µg/ml in the 1st trial and from 0.5 to 20 ug/ml in the 2nd trial. The cells were treated for 19 hours at 37^{o} C. Vehicle control (DMSO) and positive control (2-acetyl-aminofluorene, 1.0 µg/ml) cultures were included in the assay. There were 3 cultures per treatment level. There was no treatment-related increase in unscheduled DNA synthesis as ascertained by autoradiography. The positive control was functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/30/10)

** 53088-0156; 247390; " JAU 6476: Test on Unscheduled DNA Synthesis in Rat Liver Primary Cell *In Vivo*"; (B. Herbold; Bayer AG, Department of Toxicology, D-42096 Wuppertal, Germany; Report No. 109253; 6/29/99); Eight Sprague-Dawley male rats/group received a single oral dose of 0 (aqueous 0.5% cremophor), 2500 or 5000 mg/kg of JAU 6476 (batch no. NLL 6096-12; purity: 99.7%) by gavage. Hepatocytes from 4 animals/group/time point were isolated at 4 and 16 hours post-dosing. Viability was determined by trypan blue dye exclusion and ranged from 70 to 83%. After attachment, cells were exposed to (methyl-^{3}H) thymidine for 4 hours followed by an overnight incubation with unlabelled thymidine. Three slides per animal were scored, 50 cells per slide. No increase in the net nuclear grain counts was evident at any dose level or sampling time. **No adverse effect indicated**. Positive controls were functional. **Study Acceptable**. (Moore, 4/30/10).

NEUROTOXICITY

Rat Acute Neurotoxicity Study

** 53088-0160; 247397; "An Acute Oral Neurotoxicity Screening Study with Technical Grade JAU 6476 in Wistar Rats"; (L.P. Sheets, S.G. Lake; Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS; Report No. 109250; 2/3/00); Twelve Wistar rats/sex/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% methylcellulose/0.4% Tween 80), 200, 750, or 2000 mg/kg of JAU 6476 technical grade (batch no. 898803005; purity: 97.6%). Functional observational battery and motor activity evaluations were performed prior to treatment, at 4 hours post-dose and on days 7 and 14. No deaths resulted from the treatment. There was no treatment-related effect upon mean body weights. Increased perianal staining was noted for the both sexes in the 750 and 2000 mg/kg groups and in the males of the 200 mg/kg group during the first several days post-dose. The Functional Observational Battery did not reveal any treatment-related effects. The motor and locomotor activities of both sexes in the 2000 mg/kg group and the males in the 750 mg/kg group were lower than those of the control group on day 0. No treatment-related effect was noted upon the brain weights. No neurological lesions were evident in the microscopic examination. **No adverse effect was indicated. Rat Acute Neurotoxic NOEL:** (M) <200 mg/kg (based upon the increased perianal staining for the males in the 200 mg/kg group),

(F) 200 mg/kg (based upon the perianal staining for the females in the 750 mg/kg group); **Study acceptable.** (Moore, 5/4/10)

Rat Subchronic Neurotoxicity Study

** 53088-0159; 247396; "A Subchronic Oral Neurotoxicity Screening Study with Technical Grade JAU 6476 in Wistar Rats"; (S.G. Lake; Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS; Report No. 109968; 4/12/01); Twelve Wistar rats/sex/group were dosed orally by gavage with 0, 100, 500 or 1000 mg/kg/day of JAU 6476 technical grade (batch nos. 898803005, 6233/031; purity: (898803005) 97.6%, (6233/031) 98.1%), 5 days/week for 13 weeks. One female in the 500 mg/kg group was found dead on day 55. Another female in the 500 mg/kg group and one female in the 1000 mg/kg group were misdosed and died on days 85 and 51, respectively. The mean body weight gains of the males in the 500 and 1000 mg/kg groups were lower than those of the control group over the course of the study (NS). There was no apparent treatment-related effect upon the mean food consumption. The Functional Observational Battery and motor activity assessments and the ophthalmological examination did not reveal any treatment-related effects. In the necropsy examination, no treatment-related effect was noted upon the brain weights. In the micropathology, no treatment-related lesions were evident. **No adverse effect indicated. Rat Subchronic Oral Neurotoxicity NOEL:** (M/F) 1000 mg/kg/day (based upon the lack of treatment-related effects at the highest dose tested); **Study acceptable.** (Moore, 5/4/10)

SUBCHRONIC STUDIES

Rat 4-Week Dietary Toxicity Studies

53088-0172; 247410; "JAU 6476: Study for Subacute Toxicity in Rats (Feeding Study for 4 Weeks)"; (P. Andrews, A. Romeike; Bayer AG, Department of Toxicology, 42096 Wuppertal, Germany; Report No. 109061; 3/25/97); Five Wistar rats/sex/group received 0, 400, 2000 or 10000 ppm of JAU 6476 (batch no. NLL 6096-4; purity: 99.5%) in the diet for 4 weeks ((M) 0, 18.6, 145.7, 951.7 mg/kg/day, (F) 0, 18.8, 151.0, 1032.5 mg/kg/day, values based on analytical determinations). The mean body weights and food consumption of the 10000 ppm males were less than the control values throughout the study (NS, $p<0.05$ or 0.01). There was no treatment-related effect noted in the hematology and urinalysis. In the clinical chemistry evaluation, the mean serum urea levels in both sexes of the 10000 ppm group were greater than the control values ($p<0.01$). The mean cholesterol value of the 10000 ppm females was greater than that of the control group ($p<0.05$). The mean T4 level of the 10000 ppm females was less than the control value ($p<0.05$). The mean TSH level of the 10000 ppm females was greater than the control level ($p<0.05$). In the examination of the liver, the mean cytochrome P450 values of both sexes in the 10000 ppm group were elevated above those of the control group ($p<0.01$). In the hepatic enzyme assays, the 7-ethoxycoumarin deethylase activity of the 10000 ppm males was elevated above the control level ($p<0.01$). The epoxide hydrolase activities of both sexes in the 400, 2000 and 10000 ppm groups were elevated above the control activities (NS, $p<0.05$ or 0,01). The glutathione-S-transferase activities in the liver of both sexes in the 2000 and 10000 ppm groups were greater than the control values ($p<0.05$ or 0.01). The UDP-glucuronyltransferase activities of both sexes in the 10000 ppm group were greater than the control values ($p<0.05$ or 0.01). In the necropsy examination, the mean absolute and relative liver weights of the 10000 ppm females were greater than the control values ($p<0.05$ or 0.01). The mean relative testes weight of the 10000 ppm males was greater than that of the control ($p<0.01$). In the cell proliferation assay, the number of PCNA positive cells/1000 cells in the livers of both sexes in the 10000 ppm group were less than the control values. The proliferative indices in the renal medulla of both sexes in the 10000 ppm group and in the renal cortex of the 10000 ppm males were greater than the control values. This increase was attributed to treatment-related toxicity rather than an oncogenic response. In the histopathology examination, basophilic tubules were noted in the kidneys of both sexes in the 10000 ppm group ((M) 0: 1/5 vs. 10000: 5/5, (F) 0: 0/5 vs. 10000: 3/5). Tubular dilation was also noted in the kidneys of both sexes in the high dose group ((M) 0: 0/5 vs. 10000: 5/5, (F) 0: 0/5 vs. 10000: 2/5). **No adverse effect indicated. Rat 4-Week Dietary**

Toxicity NOEL: (M/F) < 400 ppm ((M) < 18.6 mg/kg/day, (F) < 18.8 mg/kg/day) (based upon increased epoxide hydrolase activity in the livers of both sexes in the 400 ppm group); **Study supplemental.** (Moore, 12/29/09)

53088-0173; 247411; "JAU 6476: Study for Subacute Oral Toxicity in Rats (4-Week Study Comparing Different Modes of Administration)"; (P. Andrews, E. Hartmann, U. Schmidt; Bayer AG, Department of Toxicology, 42096 Wuppertal, Germany; Report No. 109062; 12/15/98); Five Wistar rats/sex/group received 0 or 10000 ppm of either JAU 6476 (neat) (batch no. NLL6096-12, purity: 99.5%) or JAU 6476 10 VM 06233/0018 (silica-stabilized) (batch no. 898709001, a.i.: 8.25%) in the diet for 4 weeks (dietary study) ((M) 0, 1078, 1038 mg/kg/day, (F) 0, 850, 1067 mg/kg/day) . In a second cohort, five rats/sex/group were dosed orally by gavage with 0 or 1000 mg/kg/day of JAU 6476 (batch no. NLL6096-12, purity: 99.5%) for 4 weeks (gavage study). No deaths resulted from the treatment. The mean body weights of the males in the 10000 ppm neat were less than that of the control group throughout the treatment period (NS, $p<0.05$). There was no apparent treatment-related effect on food consumption or water uptake in any of the groups. No treatment-related effect was noted in the hematology evaluation of the gavage study animals and the urinalysis of both the dietary and gavage study animals. In the clinical chemistry evaluation, the mean serum urea concentration of the 1000 mg/kg males in the gavage study was greater than the control value ($p<0.01$). The mean serum albumin concentration of the 1000 mg/kg females was lower than that of the control ($p<0.01$). Although some of the serum enzyme parameters were elevated for the treated animals, the effects were not deemed to be toxicologically significant. In the hepatic enzyme assays, the 7-ethoxycoumarin deethylase activities of the10000 ppm males (both neat and stabilized) and the 1000 mg/kg males were elevated above the control level ($p<0.05$ or 0.01). The aldrin epoxidase activities of these same animals were lower than the control values (NS, $p<0.01$). The epoxide hydrolase activities of both sexes in the 10000 ppm group (both neat and stabilized) and of both sexes in the 1000 mg/kg group were elevated above the control activities ($p<0.05$ or 0.01). The glutathione-S-transferase activities in the liver of both sexes in the 10000 ppm group (neat) and the 1000 mg/kg group and the males in the 10000 ppm group (stabilized) were greater than the control values ($p<0.05$ or 0.01). The UDP-glucuronyltransferase activities of both sexes in the 1000 mg/kg group and the males in the 10000 ppm group (stabilized) were greater than the control values ($p<0.05$ or 0.01). In the pharmacokinetic study, the concentration of the test material in the serum was greatest for the animals in the gavage study. The animals receiving the neat test material in the diet had higher serum levels of the active ingredient than did the animals dosed with the stabilized material throughout the study. The concentration of the metabolite, SXX 0665, ranged from undetectable to five percent of the parent compound. The mean absolute and relative liver weights of the 1000 mg/kg females and the mean relative liver weight of the 10000 ppm females (neat) were greater than the control values ($p<0.05$ or 0.01). In the histopathology, an increased incidence of basophilic tubules was noted in the kidneys of both sexes in the 10000 ppm group (neat) and the 1000 mg/kg group. **No adverse effect indicated.** Treatment with the neat test material in the diet resulted in a more toxic response at a comparable dose level than did the stabilized material. The toxic effects exhibited by the animals in the gavage study were comparable to the those observed in the animals treated in the diet with the neat test material. **Study supplemental** (non-guideline study). (Moore, 12/30/09)

Rat Subchronic Oral Toxicity Study

53088-0104; 247328; "JAU 6476: Study on Subchronic Toxicity in Wistar Rats (Administration by Gavage over 14 Weeks with a Subsequent Recovery Period over 4 Weeks)"; (U. Wirnitzer, E. Hartmann; Bayer AG, Department of Toxicology, 42096 Wuppertal, Germany; Report No. 109095; 4/22/99); Ten Wistar rats/sex/group were dosed orally by gavage with 0, 20, 100 or 500 mg/kg/day of JAU 6476 (prothioconazole technical) (batch no. 898803005; purity: 97.6%) for 14 weeks. The vehicle was aqueous 0.5% tylose. A recovery cohort of 10 animals/sex/group were treated in the same manner with 0 or 500 mg/kg/day for 14 weeks and then were maintained without treatment for another 4-week recovery period. A satellite cohort of 5 animals/sex/group was dosed with 0, 20, 100 or 500 mg/kg/day of the test material in the same manner for 30 days. This cohort was evaluated for potential immunotoxic effects. Three males and one female in the

500 mg/kg group died or were euthanized in moribund condition. Two of these deaths were attributed to misdosing and one as a consequence of blood collection. In addition, one female in both the control and 100 mg/kg groups died as a consequence of blood collection. There was no treatment-related effect upon the mean body weights and food consumption. Water uptake was increased for both sexes in the 500 mg/kg group over the course of the study. No treatment-related effects were noted in the hematology evaluation and the urinalysis at 5 and 14 weeks of treatment and 4 weeks of recovery. In the clinical chemistry evaluation, the mean serum cholesterol values of both sexes in the 500 mg/kg group were elevated above the control values at both 5 and 14 weeks (NS, $p<0.05$ or 0.01). The serum triglyceride levels for both sexes in the 500 mg/kg group were less than the control values at 5 and/or 14 weeks of treatment (NS, $p<0.05$ or 0.01). The mean serum urea of the 500 mg/kg group males was greater than that of the control at 14 weeks of treatment ($p<0.01$). In the hepatic enzyme assays, the 7-ethoxycoumarin deethylase activity of the 500 mg/kg males was greater than the control level after 14 weeks of treatment ($p<0.01$). The aldrin epoxidase activities of all of the males in all of the treated groups were lower than the control value ($p<0.01$). The epoxide hydrolase activities of both sexes in the 500 mg/kg group were elevated above the control activities ($p<0.05$ or 0.01). The UDP-glucuronyltransferase activities of the males in the 500 mg/kg group was greater than the control value ($p<0.05$). Cytochrome P450-dependent hydroxylation of testosterone in the 16a and the 2a positions was less for the males in the 500 mg/kg group in comparison to the control values. Hydroxylation in the 2B and 6B positions was increased in both sexes of the 500 mg/kg group. In the pharmacokinetic study, the concentration of the parent compound in the blood at 1 hour post-dose appeared to reach a plateau between the intermediate and the highest dose level. However, no evaluation of the time to peak plasma concentration was performed. In the immunotoxicity study, there was no treatment-related effect on the number of splenic cells and the antibody titer was not affected by the treatment. Increased macrophagic activity was noted in the 100 and 500 mg/kg males and in the 500 mg/kg females. This response was related to the presence of cell destruction in the treated animals. In the splenic distribution of immuno-relevent cell populations, only the pan-B cells and antigen-presenting cells in the 500 mg/kg females were elevated above control levels ($p<0.05$). In the necropsy examination, the mean absolute and relative liver weights of the 500 mg/kg females were greater than the control values ($p<0.05$ or 0.01). In the histopathology, hepatocellular hypertrophy and cytoplasmic changes were evident in the livers of both sexes in the 500 mg/kg group (for both lesions: (M) 0: 0/10 vs. 500: 6/10, (F) 0: 0/10 vs. 2/10). Single cell necroses were noted in the livers of the 100 and 500 mg/kg males (0: 0/10 vs. 500: 2/10). Congestion was also noted in the livers of the 500 mg/kg males (0: 0/10 vs. 500: 2/10). A dose-related incidence of basophilic tubules was noted in the three male treatment groups (0: 5/10 vs. 20: 8/10, 100: 8/10, 500: 9/10). No treatment-related lesions were noted in the recovery animals. **Possible adverse effect:** single cell necrosis in the liver. **Rat Subchronic Oral Toxicity NOEL: (M)** 20 mg/kg/day (based upon the incidence of single cell necrosis in the livers of the 100 mg/kg males; **(F)** 100 mg/kg/day (based upon the presence of lesions in the livers of the 500 mg/kg females); **Study acceptable.** (Moore, 1/5/10)

Rat 21-day Repeated Dose Dermal Toxicity Study

53088-0108; 247332; JAU 6476: Study for Subacute Dermal Toxicity in Rats (Four-Week Treatment Period); (F. Krotlinger and E. Hartmann; Bayer AG, Institute for Toxicology, D-42096 Wuppertal, Germany; Report No. 30115; 7/26/00); The skin of 10 Wistar rats/sex/group was exposed to 0, 100, 300 or 1000 mg/kg/day of JAU 6476 (Prothioconazole technical) (batch no. FI. 6233/0031; purity: 98.5%) 6 hours/day, 5 days per week for 3 weeks followed by another week of 6 hours/day. The test material was placed on a piece of gauze moistened with water and the gauze was placed on the skin. No deaths resulted from the treatment. The mean body weights or food consumption were not affected by the treatment. The hematology, clinical chemistry, and ophthalmology evaluations did not reveal any treatment-related effects. There was no effect upon the absolute or relative organ weights in the necropsy examination. No treatment-related lesions were noted in the histopathology. No dermal lesions were evident at the site of application. The concentrations of the test material and the metabolite SXX 0665 in the plasma were at or below the limits of detection. **No adverse effect indicated. Reported Rat Repeated Dosing Dermal Toxicity NOEL:** (M/F) 1000 mg/kg/day (based upon the lack of treatment-related effects on the

1000 mg/kg treatment group); **Reported Dermal Irritation NOEL:** (M/F) 1000 mg/kg/day (based on the lack of dermal irritation at the site of application on the 1000 mg/kg treatment group); **Study unacceptable,** possibly upgradeable to acceptable with a more detailed description of how the test material was moistened. (Moore, 1/26/10)

Mouse Subchronic Oral Toxicity Study

53088-0171; 247409; "JAU 6476: Dose Range-Finding Study in CD-1 Mice (Administration by Gavage over 14 Weeks)"; (U. Wirnitzer, E. Hartmann; Bayer AG, Department of Toxicology, 42096 Wuppertal, Germany; Report No. 109063; 3/2/99); Ten CD-1 mice/sex/group were dosed orally by gavage with 0, 25, 100 or 400 mg/kg/day of JAU 6476 (prothioconazole technical) (batch no. 898803005; purity: 97.6%) for 14 weeks. One male in the 400 mg/kg group died as a consequence of a gavaging error. One male in the 400 mg/kg group and two females each in the control and 25 mg/kg groups died as a result of bleeding trauma. There was no treatment related- effect upon mean body weights or food consumption. No effect was noted on the hematology parameters. In the clinical chemistry, the total bilirubin levels in the serum of both sexes in the 400 mg/kg group were less than the control values ($p<0.01$). The serum albumin level of the 400 mg/kg males was less than that of the control ($p<0.01$). In the necropsy, the mean absolute and relative liver weights of both sexes in the 400 mg/kg group, the mean relative liver weights of both sexes in the 100 mg/kg group and the mean relative liver weight of the males in the 25 mg/kg group were greater than the control group values ($p<0.0$ or 0.01). The 7-ethoxycoumarin deethylase,7-ethoxyresorufin deethylase, aldrin epoxidase and glutathione-S-transferase activities in the livers of the females in the 25, 100 and 400 mg/kg groups were greater than the control values ($p<0.05$ or 0.01). The epoxide hydrolase and UDP-glucuronyltransferase activities in the livers of the 400 mg/kg females were greater than the control values ($p<0.05$ or 0.01). For the males, although the activity levels for these liver enzymes were elevated in the higher dose groups, the dose-response was not apparent. In the histopathology, cytoplasmic changes and hepatocellular hypertrophy were noted in the livers of both sexes in the 100 and 400 mg/kg groups. Focal necroses and vacuolation were evident in the livers of 3 and 6 males, respectively, in the 400 mg/kg group. Fatty change was noted in the livers of 6 females in the 400 mg/kg group. **Possible adverse effect:** focal necrosis in the liver; **Mouse Subchronic Oral Toxicity NOEL;** (M/F) < 25 mg/kg/day (based upon treatment related-effects on the livers of both sexes in the 25 mg/kg group); **Study supplemental** (ophthalmology examinations were not performed, a limited number of parameters were evaluated in the hematology and clinical chemistry and only a select number of tissues were examined in the histopathology). (Moore, 3/29/10)

Dog Subchronic Oral Toxicity Study

53088-0106; 247330; "Technical Grade JAU 6476: A Subchronic Oral Gavage Study in the Beagle Dog"; (R.D. Jones, B.P. Stuart; Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS; Report No. 109442; 11/30/01); Four beagle dogs/sex/group were dosed orally by gavage with 0, 25, 100 or 300 mg/kg/day of JAU 6476 (Prothioconazole technical) (batch no. 6233/0031; purity: 98.4% (2/99)) 5 days/week for 3 months. A recovery cohort of 4 animals/sex/group were dosed in the same manner with 0 or 300 mg/kg and then maintained on study for another 2 months without treatment. No deaths resulted from the treatment. The mean body weight gain of the males in the 300 mg/kg group was lower than that of the control group over the course of the treatment period. No treatment-related effect on food consumption was evident. No treatment-related effect was noted in the electrocardiograms and blood pressure measurements and the neurological and ophthalmological evaluations. The hematology evaluation and urinalysis did not reveal any apparent treatment-related effect. In the clinical chemistry evaluation, the serum cholesterol levels in the 100 and 300 mg/kg males were less than the control values during the study (NS, $p<0.05$). The T4 and TSH levels in the serum of the 300 mg/kg females were less than those of the control group throughout the treatment period (NS, $p<0.05$). The serum alanine amino transferase activity of the females in the 300 mg/kg group was elevated throughout the treatment period ($p<0.05$). The activity level was still slightly elevated throughout the recovery period ($p<0.05$). Serum alkaline phosphatase activity level of the 300 mg/kg females was also elevated throughout the treatment period and was elevated during the

recovery period ($p<0.05$). No treatment-related effect on the N-demethylase and O-demethylase activities and the cytochrome P450 content in the livers of the study animals was noted at the termination of the main study. Epoxide hydrolase activities in the livers of the 100 and 300 mg/kg females were greater than the control value at the termination of the dosing period ($p<0.05$ or 0.01). In the testosterone metabolism assay, the formation of 6B-OH-T (CYP 3A) was increased in a dose-related manner for the females (NS). No effect was noted on the renal enzymes. Recovery of JAU 6476 and SXX 0665 was greater in the liver than in the kidney. SXX 0665 constituted approximately one tenth that of the parent compound. The concentrations of the two compounds were greater in the livers and kidneys of the females than the males. The mean absolute liver and kidney weights of the 300 mg/kg females and the mean relative liver and kidney weights of both sexes in the 300 mg/kg group in the main study were greater than the control values (NS, $p<0.05$). The mean absolute and relative thymus weights of the 300 mg/kg females were greater than those of the control group (NS, $p<0.05$). No effect was noted for the recovery cohort. In the histopathology, epithelial cell degeneration in the proximal tubules of the kidney was noted for 3 males in the 300 mg/kg group. Chronic inflammation was evident in the kidneys of 3 males and one female each in the 100 and 300 mg/kg groups. This inflammation was present in two males and one female in the 300 mg/kg group of the recovery cohort. Reactive ovaries (increased incidence of polyovular follicles) were noted in one female in the 100 mg/kg group and two females in the 300 mg/kg group. **Possible adverse effect:** degeneration of epithelial cells in the proximal tubules of the kidneys and chronic inflammation in the kidneys. **Dog Subchronic Oral Toxicity NOEL:** (M/F) 25 mg/kg/day (based upon lesions in the kidneys of both sexes in the 100 mg/kg group); **Study acceptable.** (Moore, 2/1/10)

METABOLISM

Metabolism, Rat

53088-0165; 247403; "[^{14}C] JAU 6476: Rat Metabolism Part 1 of 2: Investigation of the Biokinetic Behaviour and the Metabolism (ADME) in the Rat with [Triazole-UL-^{14}C]- and [Phenyl-UL-^{14}C] JAU 6476"; (K. Justus; Bayer AG, Agrochemicals Division, Crop Protection Development, Institute for Metabolism Research and Residue Analysis, D-51368 Leverkusen, Germany; Report No. MR-251/01; 12/11/01); Ten tests were performed in which Wistar rats of either sex were dosed orally by gavage with 2, 5 or 150 mg/kg of [Triazole-UL-^{14}C] JAU 6476 (batch no. 10708/1, specific radioactivity: 52.3 uCi/mg, radiochemical purity: >99% (test nos. 1 - 4), > 98% (test no. 16), chemical purity: >99%) or [Phenyl-UL-^{14}C] JAU 6476 (batch no. 11403/1, specific radioactivity: 80.3 uCi/mg, radiochemical purity: >99%, chemical purity: >99% (test 8), batch no. 12268/1, specific radioactivity: 99 uCi/mg, radiochemical purity: >98%,, chemical purity: >98% (test nos. 9, 11 and 12), batch no. 14015/1, specific radioactivity: 126.5 uCi/mg, radiochemical purity: >99%, chemical purity: >99% (test no. 18. Non radiolabeled JAU 6476 (batch no. 960226ELB01, purity: 99.8% (test no. 3), batch no. M00729, purity: 99.4% (test nos. 9, 11, 16, 18), batch no. 898002902, purity: 99.5% (test no. 12)) was used to adjust the specific activity of an administered dose and was used to dose the animals in the multiple dosing regimen. In two of the tests, males or females were dosed daily for 14 or 15 days with 2 mg/kg of the unlabeled test material followed by a single dose of the labeled material. Expired air was recovered up to 48 hours post-dose in Test No. 8. Urine and feces samples were recovered at specified time intervals up to 48 or 168 hours post-dose in all of the tests except for Tests Nos. 4 and 11. Bile was collected up to 48 hours post-dose (test no. 4) and up to 6 hours post-dose (test no. 9). Plasma was recovered up to 48 hours post-dose in all tests except for Nos. 4, 8, and11. The primary excretory route of radioactivity was via the feces with 73 to 94% of the administered dose recovered by 48 hours post-dose. Recovery in the urine constituted 3 to 15% of the administered dose over the same time interval. There were no apparent differences arising from the different dosing regimens or between the sexes. In test no. 4, 90% of the radioactivity was recovered in the bile in the first 48 hours post-dose. An additional 1% was recovered in the feces. Approximately 92% of the administered dose was absorbed within the 1st 24 hours (estimated from bile and renal excretion data in study no. 4). In the other tests, approximately 0.4 to 3% % of the radioactivity was retained in the tissues at 48 hours post-dose. The liver was the primary organ in which radioactivity was recovered at 48 or 168 hours post-dose. The range of values for the pharmacokinetic parameters were as follows; $t_{1/2}$ (absorption): 0.011 to 0.233 hours, $t_{1/2}$

(elimination, phase 1): 0.350 to 0.926 hours, $t_{1/2}$ (elimination, phase 2): 8.08 to 18.7 hours, $t_{max:}$ 0.18 to 0.71 hours, $C_{max:}$ (2 and 5 mg/kg treatments) 0.35 to 0.92 ug/ml, (150 mg/kg treatment) 45.0 and 69.8 ug/ml). Metabolism of the parent compound included desulfuration and hydroxylation of the phenyl ring followed by conjugation with glucuronic acid. The primary metabolite which was recovered was JAU 6476 Desthio (SXX 0665) which constituted 18 to 24% of the radiolabel recovered from the females and 5 to 18% from the males. The glucuronide conjugate was the predominant metabolite recovered in the bile. Cleavage of the parent molecule was not readily observed. Recovery of radiolabeled triazole was a small fraction of the administered dose. Seven to 21% of the radiolabeled moieties recovered in the urine and feces were not identified. Twenty six to 30% of the recovered radiolabel in the bile could not be identified. The authors of the report attributed this high percentage of unknown metabolites to the difficulty of extracting the radiolabel from the fecal solids. No rationale was provided for the high percentage of unknown metabolites reported in the bile. **Study acceptable.** (Moore, 5/17/10)

53088-0163; 247400; "[^{14}C] JAU 6476: Rat Metabolism Part 2 of 2: Distribution of the Total Radioactivity in Rats Determined by Quantitative Whole Body Autoradiography (QWBA) with [Triazole-UL-^{14}C]- JAU 6476"; (K. Justus; Bayer AG, Agrochemicals Division, Crop Protection Development, Institute for Metabolism Research and Residue Analysis, D-51368 Leverkusen, Germany; Report No. MR-437/01; 12/11/01); Eight Wistar rats/sex were dosed with 4 mg/kg of [Triazole-UL-^{14}C] JAU 6476, batch no. 10708/1, specific radioactivity: 52.3 uCi/mg, radiochemical purity: >99% (test no. 5), > 98% (test no. 17) , chemical purity: >99%). Non-radiolabeled JAU 6476 (batch no. 960226ELB01, purity: 99.8% (test no. 5), batch no. 898002902, purity: 99.5% (test no. 17) was used to adjust the specific activity of the administered dose. One animal/sex/time point was euthanized at 1, 4, 8, 24, 48, 72, 120 and 168 hours post-dose. Whole body autoradiographic procedures were used to quantify the radiolabel in specific tissues over the course of the study. Urine and feces were collected at specified time points from surviving animals through to the termination of the study. By 24 hours post-dose, greater than 95% of the administered dose was recovered in the excretory products. Feces constituted approximately 93 to 96% of the recovered radiolabel in the males and 80 to 94% in the females. The highest concentrations of radiolabel were identified in the liver, renal medulla and cortex, brown and perirenal fat, thyroid gland and the adrenal gland. The time-to-peak tissue levels was one hour post-dose in the males. In the females a biphasic concentration pattern was observed with peak levels at 1 and 8 hours post-dose. No appreciable radioactivity was localized in the central nervous system. **Study supplemental.** (Moore, 5/19/10)

Monkey Toxicokinetic Study

53088-0167; 247405; "An Exploratory Study to Determine the Rate and Route of Elimination of JAU 6476 When Administered Intravenously or Dermally to Male Rhesus Monkeys"; (C.A. Sebesta; Charles River Laboratories, Discovery and Development Services, Worcester, MA; Report No. QEAZ-172-02-370; 10/8/03, amended, 10/10/03); One male rhesus monkey each was treated by iv injection or by dermal application with radiolabeled JAU 6476.. In the iv injection treatment, the monkey was dosed with 240 ug of [Phenyl-UL-^{14}C] JAU 6476 (no batch number; specific activity: 100.8 uCi/mg; radiochemical purity: 98.0%) and urine, cage washings and feces were collected periodically up to 8 day post-dose. In the dermal treatment, the skin of the monkey was exposed to 248 ug at 10.3 ug/cm^2 (25.2 uCi) of JAU 6476 SC480 containing [Phenyl-UL-^{14}C] JAU 6476 (no batch no.; specific activity: 0.504 uCi/ul, radiochemical purity: 96.1%) for 8 hours. Any residual test material on the application area was removed at that time. Urine, cage washings and feces were then collected periodically up to 8 days post-dose. In the iv treatment, 56% of the administered dose was excreted in the urine (urine plus cage wash) within the first 24 hours post-dose. Eight percent was recovered in the feces during the 1st 24 hours. In the dermal treatment, a total of 3.30% of the administered dose was recovered in the excretion products up to 8 days post-dose. Eighty nine percent of the dose was accounted for in the residual skin washings after 8 hours of exposure. These results demonstrate that once the test material is in the blood circulation, its primary route of excretion is in the urine and that only a limited fraction of the test material is absorbed via the dermal route within 8 hours post-application. **Study supplemental.** (Moore, 5/25/10)

SXX 0665 (desthio-analogue of prothioconazole)

COMBINED, RAT

**** 53088-0135; 247369**; "SXX 0665: Combined Study on Chronic Toxicity and Carcinogenicity in Wistar Rats (Dietary Administration over 2 Years)"; (L. Schladt, E. Hartmann, M. Rinke; Bayer AG, Department of Toxicology, 42096 Wuppertal, Germany; Report No. 109447; 12/3/99); Fifty Wistar rats/sex/group received 0, 20, 140 or 980 ppm of SXX 0665 (batch no. 1717008/90; purity: 92.8-95.4% (based on multiple analyses over the course of the study)) in the diet for 2 years ((M) 0, 1.1, 8.0, 57.6 mg/kg/day, (F) 0, 1.6, 11.2, 77.4 mg/kg/day). An additional 10 animals/sex/group were treated in the same manner for a year. These animals were then euthanized and examined histologically for treatment-related lesions. The treatment did not adversely affect the survival of the study animals. The mean body weights of both sexes in the 980 ppm group were minimally affected by the treatment (mean values were within 10% of the control weights throughout the study). No treatment-related effect on food consumption and water uptake was evident. Although various hematological and clinical chemical parameters for the treated groups were statistically different from those of the control group at one time or another during the study, no treatment-related effects were apparent. The ophthalmological evaluations and urinalysis did not reveal any treatment-related effects. The mean relative liver weights of both sexes in the 980 ppm group were greater than the control values after 1 and 2 years of treatment ($p<0.01$ or 0.05). The mean absolute liver weights of the 980 ppm males were greater than those of the control group after both 1 and 2 years of treatment ($p<0.01$ or 0.05). In the histopathology, the liver was the primary target organ. Hepatocellular vacuolation was noted in the livers of both sexes in the 980 ppm group and in the males in the 980 ppm group after both 1 and 2 years of treatment. Centrilobular fatty changes were evident in the livers of the 980 ppm males after 1 year of treatment and in the livers of the 140 and 980 ppm males after 2 years of treatment. An increased incidence of periportal fatty changes was noted in the livers of the 980 ppm females after 1 year of treatment. After 2 years of treatment, the incidence of this effect demonstrated less of a dose-relationship. Cytoplasmic change and hepatocellular hypertrophy were evident in the livers of both sexes in the 980 ppm group after 2 years of treatment. In addition, hyperplasia of the follicular epithelium was noted in the thyroids of the 980 ppm males after 1 year and focal C-cell hyperplasia in the thyroids of this group after 2 years of treatment. An increased incidence of colloidal mineralization was evident in the thyroids of the 980 ppm females after both 1 and 2 years of treatment. An increased incidence of focal adrenocortical hyperplasia and radiculoneuropathy in the spinal cord was noted for the females in the 980 ppm group. The thyroid lesions were attributed to altered liver metabolism and deemed to be a secondary effect. Radiculoneuropathy was not evident for the males and no concomitant effects were noted in the peripheral nervous system. **Possible adverse effect:** fatty changes in the liver; **Rat Chronic Toxicity Dietary NOEL:** (M) 20 ppm (1.1 mg/kg/day) (based upon lesions in the liver of the 140 ppm treatment group), (F) 140 ppm (11.2 mg/kg/day) (based upon lesions in the liver, thyroid and adrenal gland of the 980 ppm group); **no oncogenic potential was apparent. Study acceptable.** (Moore, 4/12/10)

CHRONIC TOXICITY, RAT

See Combined, Rat above.

CHRONIC TOXICITY, DOG

Study not submitted.

ONCOGENICITY, RAT

See Combined, Rat above.

ONCOGENICITY, MOUSE

** 53088-0134; 247367, 247368; "SXX 0665: Oncogenicity Study in B6C3F1 Mice (Dietary Administration over 2 Years): (U. Wirnitzer, M. Rinke; Bayer AG, Department of Toxicology, 42096 Wuppertal, Germany; Report Nos. 30045-1, 30045; 7/20/00, addendum:10/28/02); Sixty B6C3F1 mice/sex/group received 0, 12.5, 50 or 200 ppm of SXX 0665 (batch no. 1717008/90; purity: 93.1%) in the diet for 2 years ((M) 0, 3.1, 12.8, 51.7 mg/kg/day, (F) 0, 5.1, 20.3, 80.0 mg/kg/day). Survival of the study animals was not affected by the treatment. The mean body weights, food consumption and water uptake were not affected by the treatment. The hematology and clinical chemistry parameters were not affected by the treatment. In the necropsy, the mean relative liver weights of both sexes in the 200 ppm group at termination were greater than the control values (NS, $p<0.05$). In the histopathology, hepatocellular vacuolation and periacinar fat staining was noted in the livers of the 50 and 200 ppm males after one year of treatment. The incidence of periacinar fat staining in the livers of the 200 ppm males was greater than the control group after two years of treatment ($p<0.05$). No hepatocellular vacuolation was apparent after 2 years. In the females, cytoplasmic hypertrophy was evident in the livers of the 50 and 200 ppm animals after one year of treatment. After 2 years of treatment, an increased incidence of periacinar fat staining was noted in the livers of the 50 and 200 ppm females ($p<0.001$ or 0.01). Hepatocellular hypertrophy was not apparent in the livers of these animals. **No adverse effects were evident. Mouse Chronic Dietary NOEL:** (M/F) 12.5 ppm ((M) 3.1 mg/kg/day, (F) 5.1 mg/kg/day) (based upon the incidence of periacinar fat staining in the livers of both sexes of the 50 ppm group), **no oncogenicity was evident. Study acceptable**. (Moore, 4/5/10)

REPRODUCTION, RAT

**** 53088-0127; 247352**; " Two-Generation Dietary Reproduction Study in Rats using SXX 0665"; (D.A. Eigenberg; S.G. Lake; Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS; Report No. 109835; 12/4/01); Thirty Sprague-Dawley rats/sex/group in the F0 generation received 0, 40, 160, or 640 ppm of SXX 0665 technical (batch no. 1717008/90; purity: 95.6% (3/91), 93.6% (10/91), 92.8% (7/92), 93.0% (2/93)) in the diet for a 10-week premating period, up to a 3-week mating period and 3 weeks both for the gestation and lactation periods. At that time, 30 F1 animals/sex/group were selected as parents and treated for an additional 10 weeks, followed by mating and 3 weeks each for gestation and lactation of the F2 generation ((M) 0, 2.7, 10.4 , 42.6 mg/kg/day, (F) premating: 0, 3.0, 12.0, 49.5 mg/kg/day, gestation: 0, 2.5, 10.0, 41.2 mg/kg/day, lactation: 0, 4.8, 18.6, 72.6 mg/kg/day). No apparent treatment-related effects were noted on the mean body weights and food consumption of either generation. In the necropsy evaluation, the mean absolute and relative liver weights of both sexes of the 640 ppm group in both generations were greater than the control values (NS, $p<0.05$). In the histopathology examination, increased incidence of vacuolization was noted in the livers of both sexes in the 640 ppm and in the 160 ppm males of both generations ($p<0.05$). Among the reproductive parameters evaluated, the fertility indices of the 160 and 640 ppm dams in both generations were 80% or less (note: the fertility index of the F1 control dams was unusually low). The gestation index for either generation was not affected by the treatment. An increased incidence of cannibalization of the pups was noted for dams of the 640 ppm group for both generations ($p<0.05$). The mean pup body weights of the 640 ppm group in both generations were less than those of the control animals during the lactation period (NS, $p<0.05$). No treatment-related effect was noted on the ovarian follicle counts of the F0 and F1 dams **Possible adverse effect:** incidence of dystocia at the time of parturition. **Parental NOEL:** 40 ppm ((M) 2.7 mg/kg/day) (based upon the increased incidence of vacuolization noted in the livers of the 160 ppm males); **Reproductive NOEL:** 40 ppm ((M) 2.7 mg/kg/day, (F) 2.5 mg/kg/day) (based upon the lower fertility index in the 160 ppm dams of both generations); **Developmental NOEL:** 160 ppm ((F) 18.6 mg/kg/day) (based upon lower mean pup weights of both generations during the lactation period); **Study acceptable.** (Moore, 3/17/10)

53088-0126; 247351; "Pilot Study to Establish Dose Levels for a Two-Generation Reproduction Study in Rats using Technical Grade SXX 0665 Administered Via the Diet"; (D.A. Eigenberg, H.E. Hoss; Miles Inc., Agricultural Division, Toxicology, Stilwell, KS; Report No. 103274; 9/8/92); Ten Sprague-Dawley rats/sex/group received 0, 10, 50, 1000 or 1500 ppm of SXX 0665 technical (batch no. 1717008/90; purity: 95.4% (8/90), 95.6% (3/91)) in the diet for a 4-week premating

period, a mating period and 3 weeks both for the gestation and lactation periods. The a.i. uptake was not calculated. One dam each died in the 1000 and 1500 ppm groups. The mean body weight gain of the dams in the 1500 ppm group was less than that of the control group during the gestation period ($p<0.05$). The mean food consumption of the 1000 and 1500 ppm dams was less than that of the control group during the gestation and lactation periods (NS, $p<0.05$). The mean absolute and relative liver weights of the 50, 1000 and 1500 ppm dams and the 1000 and 1500 ppm males were greater than the control values (NS, $p<0.05$). The fertility index was not affected by the treatment. However, the gestation index of the 1500 ppm dams was less than that of the control group ($p<0.05$). The mean litter sizes of both the 1000 and 1500 ppm groups were less than that of the control group. The mean body weights of the F1 offspring in the 1000 and 1500 ppm group were less than the control values during the lactation period (NS, $p<0.05$). The pup viability indices of the 1000 and 1500 ppm groups were less than the control value. Two of seven litters in the 1000 ppm group and 5 of 7 litters in the 1500 ppm group suffered cannibalized offspring. **No adverse effect indicated. Parental NOEL:** 10 ppm (based upon the greater liver weight of the 50 ppm dams); **Reproductive NOEL:** 1000 ppm (based upon the reduced gestation index demonstrated by the 1500 ppm dams); **Developmental NOEL:** 50 ppm (based upon the lower fetal body weight gain and viability index of the 1000 ppm group); **Study supplemental.** (Moore, 3/3/10)

TERATOLOGY, RAT

Teratology, Rat Oral

**** 53088-0114; 247338**; "Embryotoxicity Study (including Teratogenicity) with SXX 0665 Technical in the Rat, Report Part 1"; (H. Becker, H. Leutkemeier, K. Biedermann, O. Vogel, Ch. Terrier; RCC, Research and Consulting Company AG, CH 4452 Itingen, Switzerland; Study No. 236114; 12/11/91); Twenty five mated female Wistar rats/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% Cremophor EL), 10, 30 or 100 mg/kg/day of SXX 0665 technical (batch no. NLL 3622-2; purity: 97.4%) from day 6 through day 15 of gestation. A satellite cohort of 10 mated females/group were dosed in the same manner and then euthanized on day 16. Serum transaminase enzymes were assayed and liver histology was performed on these animals. No deaths resulted from the treatment. The mean body weight gain and food consumption of the 100 mg/kg dams was slightly less than the control values over the course of the dosing period (NS). The mean absolute and relative liver weights of the 100 mg/kg dams were greater than the control values ($p<0.05$ or 0.01). In the histpathological examination, centrilobular hypertrophy and centrilobular and/or periportal fatty changes were noted in the livers of the 100 mg/kg dams. In the fetal examination, an increased number of embryonic and fetal resorptions/litter were noted for the 100 mg/kg treatment group ($p<0.01$). Palatoschisis was noted for two fetuses in separate litters of the 100 mg/kg treatment group. This effect is sufficiently rare as to be considered an adverse effect at this treatment level. An increased incidence of supernumerary ribs was noted for fetuses in all of the treatment groups. **Possible adverse effect:** palatoschisis and supernumerary ribs in the fetuses; **Maternal NOEL:** 30 mg/kg/day (based upon the increased liver weights and presence of lesions in the liver of the 100 mg/kg dams); **Developmental NOEL:** < 10 mg/kg/day (based upon the increased incidence of supernumerary ribs in the fetuses of the 10 mg/kg group); **Study acceptable.** (Moore, 2/8/10)

**** 53088-0115; 247339**; "Supplementary Study to the Embryotoxicity Study (including Teratogenicity) with SXX 0665 Technical in the Rat, Report Part 1"; (H. Becker, K. Biedermann; RCC, Research and Consulting Company AG, P.O. Box 4452, Itingen, Switzerland; Study No. 281518; 12/6/91); Twenty five mated female Wistar rats/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% Cremophor EL), 1.0 or 3.0 mg/kg/day of SXX 0665 technical (batch no. 17005/89; purity: 94.7%) from day 6 through day 15 of gestation. No deaths resulted from the treatment. There was no treatment-related effect upon the mean body weight gain and food consumption of the treatment dams. An increased incidence of supernumerary ribs was noted for fetuses in the 3.0 mg/kg group. **Possible adverse effect:** supernumerary ribs in the fetuses; **Maternal NOEL:** 3.0 mg/kg/day (based upon the lack of a treatment-related effect on the dams in the 3.0 mg/kg group); **Developmental NOEL:** 1.0 mg/kg/day (based upon the increased

incidence of supernumerary ribs in the fetuses of the 3.0 mg/kg group); **Study acceptable.** (Moore, 2/10/10)

53088-0112; 247336; "SXX 0665: Embryotoxicity Study on Postnatal Development of Supernumerary Ribs in Rats following Oral Administration"; (B. Holzum; Bayer AG, Department of Toxicology, D-42096 Wuppertal, Germany; Report No. 109269; 10/1/92); Thirty and 39 mated Wistar female rats were dosed orally with 0 (vehicle: aqueous 0.5% Cremophor EL) or 30 mg/kg/day, respectively, of SXX 0665 technical (batch no. 17005/89; purity: 93.9%) from day 6 through day 15 of gestation. On day 20 of gestation, 15 dams/group were euthanized and caesarean sections were performed. The remaining dams gave birth and reared their young until day 21 *post partum*. The surviving pups were maintained for another 3 weeks before being euthanized. A skeletal examination of these animals was performed. There were no treatment-related effects upon the mean body weights or food consumption of the dams. All of the litters in the caesarean cohort had at least one fetus with a malformation. An increased number of litters in the 30 mg/kg group had at least one fetus with supernumerary ribs (14^{th} with possibly a 15^{th} or 16^{th}). This effect was reflected in the increased number of fetuses with supernumerary ribs in the caesarean cohort (0: 21/147 vs. 30: 133: 148). In the weaned cohort, the gestation index was not affected by the treatment. However, the rearing and viability indices of the 30 mg/kg dams were less than the control group. All of the offspring in five of the litters in the 30 mg/kg group died between day 0 and day 7 *post-partum*. There was an increased number of pups in the 30 mg/kg group of the weaned cohort which had a 14^{th} rib. **Possible adverse effect:** skeletal malformations and supernumerary ribs; compromised viability; **Maternal NOEL:** 30 mg/kg/day (based upon the lack of treatment-related effects on the dams in the 30 mg/kg treatment group); **Developmental NOEL:** <30 mg/kg/day (based upon the incidence of skeletal malformations and supernumerary ribs in the fetuses and pups of the 30 mg/kg group); **Study supplemental** (non-guideline study). (Moore, 2/16/10)

53088-0113; 247337; "SXX 0655: Exploratory Study for Embryotoxic Effects in Rats following Oral Administration"; (M. Renhof; Bayer AG, Institute of Toxicology, D-42096 Wuppertal, Germany; Report No. 18661; 1/12/90); Twenty five mated female Wistar rats/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% Cremophor EL) or 100 mg/kg/day of SXX 0665 (batch no. E 355806; purity: 99.1%) from day 6 through day 15 of gestation. No deaths resulted from the treatment. The mean body weight gain and food consumption of the dams was not affected by the treatment. Twenty two of 23 litters in the 100 mg/kg group had malformed fetuses. Limb dysplasia, macroglossia and cleft palate were the predominate malformations. **Possible adverse effect:** fetal malformations; **Study supplemental,** exploratory study. (Moore, 2/3/10)

Teratology, Rat Dermal

**** 53088-0118; 247343**; "SXX 0665: Study for Embryotoxic Effects in Rats following Dermal Exposure"; (B. Holzum; Bayer AG, Department of Toxicology, D-42096 Wuppertal, Germany; Report No. 109280; 8/14/91); The skin of 25 mated female Wistar rats/group was exposed to 0 (vehicle: aqueous 1% Cremophor EL), 100, 300 or 1000 mg/kg/day of SXX 0665 technical (batch no. 17005/89; purity: 93.7%) for 6 hours/day from day 6 through day 15 of gestation. No maternal deaths resulted from the treatment. The mean body weight gain or food consumption of the dams was not affected by the treatment. Slight reddening of the skin was noted at the site of application for the treated animals. An increased number of litters in which at least one fetus had a supernumerary rib was noted in the 100 mg/kg group and above. **Possible adverse effect:** increased incidence of supernumerary ribs; **Maternal NOEL:** 1000 mg/kg/day (based upon the lack of a treatment-related effect in the dams of the 1000 mg/kg group); **Developmental NOEL:** < 100 mg/kg/day (based upon the increased incidence of supernumerary ribs in the fetuses of the 100 mg/kg group); **Study acceptable.** (Moore, 2/18/10)

** 53088-0119; 247344; "SXX 0665: Supplementary Study for Embryotoxic Effects in Rats following Dermal Exposure"; (K. Bartmann; Bayer AG, Department of Toxicology, D-42096 Wuppertal, Germany; Report No. 109280-1; 8/23/91); The skin of 25 mated female Wistar

rats/group was exposed to 0 (vehicle: aqueous 1% Cremophor EL), 10 or 30 mg/kg/day of SXX 0665 technical (batch no. 17005/89; purity: 94.7% (6/13/90), 94.0% (10/9/90)) for 6 hours/day from day 6 through day 15 of gestation. No maternal deaths resulted from the treatment. The mean body weight gain and food consumption of the 30 mg/kg dams during the treatment period were less than the values for the control group (NS, $p<0.05$). Signs of slight dermal irritation were evident at the site of application for the treated dams. There were no treatment-related effects upon the development of the fetuses. **No adverse effect indicated. Maternal NOEL:** 10 mg/kg/day (based upon the lower body weight gain and food consumption of the 30 mg/kg dams); **Developmental NOEL:** 30 mg/kg/day (based upon the lack of a treatment-related effect upon the fetuses in the 30 mg/kg group); **Study acceptable.** (Moore, 2/22/10)

TERATOLOGY, RABBIT

Teratology, Rabbit Oral

** 53088-0121; 247346; "SXX 0665: Study for Embroyotoxic Effects in Rabbits following Oral Administration"; (K. Bartmann; Bayer AG, Department of Toxicology, D-42096 Wuppertal, Germany; Report No. 109270; 9/6/91); Fifteen mated CHBB:HM female rabbits/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% Cremophor EL), 2.0, 10.0 or 50 mg/kg/day of SXX 0665 technical (batch no. 17005/89; purity: 94.7% (6/13/90), 94.0% (10/9/90)) from gestation day 6 through gestation day 18. No maternal deaths resulted from the treatment. The mean body weight gain of the 50 mg/kg does was less than that of the control group throughout the study ($p<0.05$). The mean food consumption of the 50 mg/kg does was less than that of the control animals. In the histopathological examination of the maternal livers, an increased incidence of reduced glycogen uptake was noted for the 10.0 and 50 mg/kg does (enhanced stainability) (0: 3/15 vs. 10.0: 7/14, 50: 9/12). Liver cell hypertrophy was evident for two does in the 50 mg/kg group. An increased incidence of round cell infiltration was exhibited in the livers of the 10.0 and 50 mg/kg does (0: 4/15 vs. 10.0: 9/14, 50: 8/12). Increased resorption of implantations was noted for all of the treatment groups. Arthrogryposis (persistent flexure or contracture of a joint) was noted for one fetus in one litter of the 2.0 mg/kg group and for 5 fetuses in 3 litters of the 10.0 mg/kg group. Cleft palate was suffered by 5 fetuses in two litters of the 50 mg/kg group. Possible adverse effect: arthrogryposis and increased resorption of implantations; Maternal NOEL: 2.0 mg/kg/day (based upon histological lesions noted in the livers of the 10.0 mg/kg dams); Developmental NOEL: < 2.0 mg/kg/day (based upon the increased resorption of implantations and fetal incidence of arthrogryposis in 2.0 mg/kg group); Study acceptable. (Moore, 2/24/10)

Teratology, Rabbit Dermal

53088-0123; 247348; "Dose Range-Finding Embryotoxicity Study (including Teratogenicity) with SXX 0665 Technical in the Rabbit (Dermal Application)"; (H. Becker, K. Biedermann; RCC, Research and Consulting Company AG, P.O. Box 4452, Itingen, Switzerland; Project No. 309554; 11/26/91); The skin of five mated Chbb:CH female rabbits/group was exposed to 0 (vehicle: aqueous 1% Cremophor), 100, 300 or 1000 mg/kg/day of SXX 0665 technical (batch no. 1717008/90; purity: 94.3%, 93.7%) for 6 hours/day from day 6 through day 18 of gestation. The mean body weight gain and food consumption of the does was not affected by the treatment. Slight to well-defined erythema and very slight to slight edema and scabbing was noted at the site of application. No treatment-related effect was evident on the development of the fetuses. No adverse effect indicated. Maternal NOEL: 1000 mg/kg/day (based upon the lack of systemic toxic effects in the 1000 mg/kg does); Developmental NOEL: 1000 mg/kg/day (based upon the lack of toxic effects on the fetuses of the 1000 mg/kg group) (note: no visceral or skeletal examination of the fetuses was performed); Study supplemental, non-guideline study. (Moore, 2/25/10)

GENE MUTATION

** 53088-0137; 247371; "SXX 0665: *Salmonella*/Microsome Test"; (B. Herbold; Bayer AG, Department of Toxicology, D-42096 Wuppertal, Germany; Report No. 108970; 9/11/90); SXX 0665 technical (batch no. 17005/89; purity: 93.7%) was directly incorporated into 4 replicate cultures/treatment level of *S. typhimurium* TA98, TA100, TA1535 and TA1537 strains at levels ranging from 0 to 5000 ug/plate (Trial #1) or 0 to 2400 ug/plate (Trials #2 and 3) under conditions of (-/+) activation and incubated for 48 hours at 37° C. An Aroclor 1254-induced rat liver S9

fraction was used to activate the test material. There was no apparent treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated.** The positive controls were functional. **Study acceptable**. (Moore, 4/13/10)

** 53088-0148; 247382; "SXX 0665: Mutagenicity Study for the Detection of Induced Forward Mutations in the V79-HPRT Assay *In Vitro*"; (S. Brendler-Schwaab; Bayer AG, Department of Toxicology, 42096 Wuppertal, Germany; Report No. 109284; 7/20/99); Chinese hamster V79 cells were exposed to SXX 0665 (batch no. 1717008/90; purity: 93.1%) at concentrations ranging from 12.5 to 250 ug/ml for 5 hours at 37^{o} C without activation and from 50 to 500 ug/ml with activation. Three trials were performed with duplicate cultures for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. No treatment-related increase in forward mutation was evident in the cultures with or w/o activation. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 4/20/10)

CHROMOSOME EFFECTS

** 53088-0150; 247384; "SXX 0665:*In Vitro* Mammalian Chromosome Aberration Test with Chinese Hamster Ovary (CHO) Cells"; (R. Gahlmann; Bayer AG, Department of Toxicology, 42096 Wuppertal, Germany; Report No. 108971; 11/2/95); Chinese hamster ovary cells were exposed to concentrations of SXX 0665 (batch no. 1717008/90; purity: 93.1%) ranging from 5 to 125 ug/ml for 4 hours under conditions of (+/-) activation. The cells were then harvested after a total incubation time of 8, 24 or 30 hours. Duplicate cultures were incubated for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used for metabolism of the test material. There was no treatment-related effect on the incidence of chromatid or chromosomal aberrations with or w/o activation. The positive controls were functional. **No adverse effect indicated**. **Study acceptable**. (Moore, 4/22/10)

DNA DAMAGE

** 53088-0153; 247387; "SXX 0665: Micronucleus Test on the Mouse"; (B.A. Herbold; Bayer AG, Department of Toxicology, 42096 Wuppertal, Germany; Report No. 108974; 2/22/93); Five Bor: NMRI mice/sex/time point were dosed by ip injection with 350 mg/kg of SXX 0665 (batch no. 1717008/90; purity: 93.1%) and euthanized 16, 24 and 48 hours after dosing. An additional 5 animals/sex/group were treated as negative or positive controls (cyclophosphamide, 20 mg/kg) and euthanized 24 hours after dosing. Bone marrow samples from the femur were examined and the numbers of micronuclei per 1000 polychromatic erythrocytes (PCE) and 1000 normochromatic erythrocytes (NCE) were determined. In addition, the number of NCE/1000 PCE was also recorded. No increase in the number of micronuclei per 1000 PCE's was noted for the treated animals. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 4/29/10) **not seconded yet**

** 53088-0157; 247391; "SXX 0665: Mutagenicity Test on Unscheduled DNA Synthesis in Rat Liver Primary Cell Cultures *In Vitro*"; (S. Bendler; Bayer AG, Department of Toxicology, D-42096 Wuppertal, Germany; Report No. 108975; 3/5/92); Primary rat hepatocyte cultures were exposed to SXX 0665 (batch no. 17005/89; purity: 93.7%) at concentrations ranging from 5.0 to 60 µg/ml. A single trial was performed. The cells were treated for 23 hours at 37^{o} C. Vehicle control (DMSO) and positive control (2-acetyl-aminofluorene, 0.5 µg/ml) cultures were included in the assay. There were 3 cultures per treatment level. There was no treatment-related increase in unscheduled DNA synthesis as ascertained by autoradiography. The positive control was functional. **No adverse effect indicated. Study acceptable.** (Moore, 5/3/10)

NEUROTOXICITY

Rat Developmental Neurotoxicity Study

** 53088-0161, -0162; 247398, 247399; "A Developmental Neurotoxicity Screening Study with Technical Grade SXX 0655 in Wistar Rats"; (D.L. Van Goethem, L.P. Sheets, H.E. Hoss, S.G. Lake; Bayer CropScience LP, Toxicology, Stilwell, KS; Report Nos. 200958, 200958-1; 3/18/04, amended, 11/28/07); Thirty mated female Wistar rats/group received 0, 40, 160 or 500 ppm of

SXX 0665 (JAU 6476 Desthio) (batch no. RUX76-105-1E; purity: 99.1%) in the diet from day 6 of gestation through day 21 of lactation (0, 3.5 to 9.9, 14.4 to 41.8, 41.6 to 125.3 mg/kg/day). Offspring from 23 litters in the control, 40 and 160 ppm groups and offspring from 21 litters in the 500 ppm group were assessed neurologically up to 70 days post-natal in the functional observational battery (FOB), measurement of motor activity, auditory startle response, passive avoidance learning and memory and water maze learning and memory assessments. The neuropathologic examination and morphometric analysis of selected neurological tissues from the pups were performed. Three dams in the 500 ppm treatment group were euthanized during delivery due to dystocia. The mean body weights and food consumption of the dams was not affected by the treatment. The mean body weights of the pups during the lactation period were not affected by the treatment. The mean body weight of the 500 ppm male pups was less than that of the control group by post-day 64 ($p<0.05$). There was no treatment-related effect on the live birth, viability or lactation indices. There was no effect on the manifestation of developmental landmarks. No treatment-related effects were noted in the FOB for either the dams or the pups. The motor activity assessment of the pups did not reveal any treatment-related effects. The auditory startle response, passive avoidance learning and memory and water maze learning and memory assessments did not indicate any treatment-related effects on the pups. No neuropathological lesions were noted in either the 21-day old pups or the 70-day old adults. Morphometric analysis of the brain of these animals did not demonstrate any treatment-related effects. **No adverse effect indicated. Maternal NOEL:** 160 ppm (14.4 to 41.8 mg/kg/day) (based upon dystocia at the time of parturition in the 500 ppm group); **Developmental Neurotoxicity NOEL:** 500 ppm (41.6 to 125.3 mg/kg/day) (based upon the lack of treatment-related effects in the offspring of the 500 ppm group); **Study acceptable.** (Moore, 5/10/10)

SUBCHRONIC STUDIES

Rat 4-Week Dietary Toxicity Study

53088-0174; 247412; "SXX 0665: Subacute Oral Toxicity Study in Rats"; (F. Krotlinger, E. Hartmann; Bayer AG, Department of Toxicology, 42096 Wuppertal, Germany; Report No. 109271; 2/18/92); Ten Wistar rats/sex/group received 0, 100, 300, or 1000 ppm of SXX 0665 (batch no. 17005/89; purity: 93.70%) in the diet for 4 weeks ((M) 0, 11, 34, 117 mg/kg/day; (F) 0, 11, 38, 121 mg/kg/day). Mean body weights and food and water consumption were not affected by the treatment. There was no treatment-related effect on thyroid hormone levels in the blood and the urinalysis and ophthalmology evaluations. In the hematology, the mean hematocrit, hemoglobin and MCH values of both sexes in the 1000 ppm group were less than the control values (NS or $p<0.05$). In the clinical chemistry assessments, the mean serum creatinine levels of both sexes in the 1000 ppm group were less than those of the control group ($p<0.05$). The mean serum cholesterol value of the 1000 ppm females was greater than the control value ($p<0.05$). In the liver tissue tests, the mean N-demethylase and O-demethylase activities of both sexes in the 1000 ppm group were greater than the control values (NS, $p<0.01$). The cytochrome P-450 content was elevated in the livers of both sexes in the 300 and 1000 ppm groups (NS, $p<0.05$, $p<0.01$). The mean triglyceride concentration in the livers of the 1000 ppm males was increased over the control level ($p<0.01$). In the necropsy examination, the mean absolute and relative liver weights of all of the treatment groups were greater than the control values for both sexes in a dose-related manner (NS, $p<0.05$ or $p<0.01$). The mean absolute and relative ovary weights of all of the treated females were greater than the control values ($p<0.01$). In the histopathology examination, males in the 1000 ppm group demonstrated more severe fatty changes in the liver (0: 0/5 vs. 1000: 5/5). This effect was less apparent for the females. The ovaries of the 300 and 1000 ppm females exhibited a greater incidence of stromal edema (0: 2/5 vs. 300: 5/5, 1000: 4/5). An increased incidence of an increased number of follicles was noted in the ovaries of the 300 and 1000 ppm females as well (0: 1/5 vs. 300: 2/5, 1000: 3/5). **Possible adverse effect:** fatty liver. **Rat 4-Week Dietary Toxicity NOEL:** (M/F)< 100 ppm ((M/F) < 11 mg/kg/day) (based upon the increased relative liver weight of the 100 ppm males and the increased absolute and relative ovary weights of the 100 ppm females). **Study supplemental,** (Non-guideline study). (Moore, 12/9/09)

Rat Subchronic Dietary Toxicity Study

**** 53088-0102; 247326**; "SXX 0665: Study on Subchronic Toxicity in Wistar Rats (Dietary Administration over 14 Weeks with a Subsequent Recovery Period over 5 Weeks)"; (L. Schladt, E. Hartmann; Bayer AG, PH-PD-P Toxicology, Carcinogenicity and Genotoxicity, 42096 Wuppertal, Germany; Report No. 109446; 11/24/99); Ten Wistar rats/sex/group received 0, 30, 125, 500 or 2000 ppm of SXX 0665 (batch no. 1717008/90; purity: 93.1%) in the diet for 14 weeks ((M) 0, 2.2, 9.7, 37.2, 162.3 mg/kg/day; (F) 0, 3.0, 12.4, 50.9, 211.5 mg/kg/day). An additional cohort of 10 animals/sex/group received 0 or 2000 ppm of the test material for 14 weeks and then were maintained for an additional 5-week recovery. No treatment-related deaths occurred during the study. The mean body weights of both sexes in the 2000 ppm group were less than those of the control animals over the course of the treatment period (NS, $p<0.05$ or 0.01). There was no apparent treatment-related effect upon food consumption. The mean hemoglobin concentrations of the 500 and 2000 ppm males were less than that of the control group after 5 weeks of treatment ($p<0.05$ or 0.01). The mean hematocrits of the 125 ppm males and of both sexes in the 500 and 2000 ppm groups were less than the control values after 5 weeks of treatment ($p<0.05$ or 0.01). These hematological effects were not apparent after 14 weeks of treatment. In the clinical chemistry evaluation, the mean serum cholesterol values of the 2000 ppm females were greater than the control values after 5 and 14 weeks of treatment ($p<0.01$). The mean serum triglyceride levels of the 500 and 2000 ppm males were less than the control values after 5 and 14 weeks of treatment (NS, $p<0.01$). The mean total bilirubin values in the serum of both sexes in the 500 and 2000 ppm groups were less than those of the control group after 14 weeks of treatment ($p<0.05$ or 0.01) (Note: the total bilirubin values for the 30 and 125 ppm females at 14 weeks were also less than the control values ($p<0.05$). These values were within the historical control range and therefore were not considered to be toxicologically relevant). The T4 levels in the blood of the 500 and 2000 ppm males after 5 weeks of treatment and in the 2000 ppm males after 14 weeks of treatment were less than the control values ($p<0.01$). In the liver tissue assays, the O-demethylase activities were elevated for the females in the 500 ppm group and for both sexes in the 2000 ppm group at the termination of the treatment and for the 2000 ppm males after the 5-week recovery period ($p<0.05$ or 0.01). The N-demethylase activities of the 500 and 2000 ppm females were greater than the control values at the conclusion of the treatment period ($p<0.05$ or 0.01). The cytochrome P-450 content in the liver was elevated for the 125 ppm females and for both sexes in the 500 and 2000 ppm groups at the termination of the treatment ($p<0.05$ or 0.01). The triglyceride content of the liver was elevated for both sexes in the 500 and 2000 ppm groups (NS, $p<0.01$) (note: the triglyceride values for the 30 and 125 ppm females were also greater than the control value, however a clear dose-response was not apparent up to 500 ppm). In the necropsy, the mean absolute and relative liver weights of both sexes in the 2000 ppm group and the relative liver weight of the 500 ppm females were greater than the control values at the termination of the dosing ($p<0.01$). The mean absolute and relative ovarian weights of the 2000 ppm females were greater than those of the control group at the end of the treatment period ($p<0.01$). No treatment-related effect on organ weights was evident at the end of the recovery period. In the histopathological examination, hepatocellular hypertrophy was evident in the livers of the 125 ppm males and of both sexes in the 500 and 2000 ppm groups at the termination of the treatment ((M) 0: 0/10 vs. 125: 5/10, 500: 7/10, 2000: 10/10, (F) 0: 0/10 vs. 500: 7/10, 2000: 9/10). This hypertrophy was still noted in the livers of the 2000 ppm males at the end of the recovery period (0: 0/10 vs. 2000: 4/10). An increased incidence of vacuolation in the liver was evident in the males in the 125 and 500 ppm groups and in both sexes in the 2000 ppm group ((M) 0: 2/10 vs. 125: 6/10, 500: 6/10, 2000: 10/10). The vacuolation persisted in the males of the 2000 ppm group after the recovery period (0: 2/10 vs. 2000: 9/10). A fatty change was noted in the midzonal/centrilobular region of the livers from the 125, 500 and 2000 ppm males (0: 0/10 vs. 125: 2/10, 500: 5/10, 2000: 10/10). This change persisted in the males of the 2000 ppm group at the end of the recovery period (0: 0/10 vs. 2000: 10/10). In the females, a diffuse and/or midzonal/centrilobular fatty change was note in the 3 of 10 females in the 2000 ppm group at the end of treatment. This effect was not evident at the end of the recovery period. **Possible adverse effect:** fatty liver. **Rat Subchronic Dietary NOEL:** (M/F) 30 ppm ((M) 2.2 mg/kg/day, (F) 3.0 mg/kg/day (based upon the presence of treatment-related histopathological effects in the

livers of the 125 ppm males and in significant increase in cytochrome P-450 content in the livers of the 125 ppm females). **Study acceptable.** (Moore, 12/14/09)

Rat 5-Day Repeated Exposure Inhalation Toxicity Study

53088-0176; 247414; "SXX 0665: Orientative Study for Subacute Inhalation Toxicity in the Rat (5 x 6-Hour Exposures)"; (J. Pauluhn; Bayer AG, Department of Toxicology, D-42096 Wuppertal, Germany; Report No. 109273; 5/21/91); Ten Wistar rats/sex/group were exposed nose-only to reported analytical concentrations of 0 (vehicle control: polyethylene glycol 400:ethanol (1:1)), 10.7, 53.9 or 234.7 mg/m^3 of SXX 0665 technical (batch no. 1717008/90; purity: 95.4%), 6 hours/day, for 5 days. The mean MMAD (GSD) values were 1.32 (1.43), 1.19 (1.36), 1.25 (1.39) and 1.23 (1.39) um, respectively. Five animals/sex/group were euthanized on day 7. The remaining animals were maintained for an additional 2 weeks as a recovery cohort. No deaths resulted from the exposure. No treatment-related effect was evident on the mean body weights during the 5-day exposure period. The females in the 234.7 mg/m^3 group gained less body weight than the control group during the 2-week recovery period. No treatment-related effect was evident in the hematology. The mean serum creatinine levels for both sexes in the 234.7 mg/m^3 were less than those of the control group ($p<0.01$). The liver enzyme activities and cytochrome P-450 and triglyceride content in the liver was not affected by the treatment. In the necropsy, no treatment-related lesions were evident and no treatment-related effect upon organ weights was noted. **No adverse effect was evident.** A NOEL value was not reported because the calculations used to document the analytical exposure concentrations were not provided. **Study supplemental.** (Moore, 5/26/10)

Rat 4-Week Repeated Exposure Inhalation Toxicity Study

53088-0177; 247415; "SXX 0665 Aerosol: Study for Subacute Inhalation Toxicity in the Rat"; (J. Pauluhn; Bayer AG, Department of Toxicology, D-42096 Wuppertal, Germany; Report No. 109283; 2/3/92); Ten Wistar rats/sex/group were exposed nose-only to reported analytical concentrations of 0, 0 (vehicle control: polyethylene glycol 400:ethanol (1:1)), 11.3, 46.8 or 228.4 mg/m^3 of SXX 0665 technical (batch no. 1717008/90; purity: 95.4%), 6 hours/day, 5 days/week for 4 weeks. The mean MMAD (GSD) values were 1.33 (1.49), 1.28 (1.47), 1.26 (1.46) and 1.28 (1.47) um, respectively. No deaths resulted from the exposure. No treatment-related effect was evident on the mean body weights. No treatment-related effect was evident in the hematology. Although certain parameters in the clinical chemistry demonstrated a significant difference in values between the control and the exposed groups, no dose-related pattern was established. In the necropsy, the mean absolute or relative organs weights were not affected by the treatment. The liver enzyme activities and cytochrome P-450 and triglyceride content in the liver were not affected by the treatment. No histological examination of the tissues was performed. **No adverse effect was evident.** A NOEL value was not reported because the calculations used to document the analytical exposure concentrations were not provided. **Study supplemental.** (Moore, 5/28/10)

Mouse Subchronic Dietary Toxicity Study

53088-0103; 247327; "SXX 0665: Dose-Range-Finding Study in B6C3F1 Mice (Dietary Administration for about 13 Weeks); (U. Wirnitzer; Bayer AG, PH-PD-P Toxicology, Carcinogenicity and Genotoxicity, 42096 Wuppertal, Germany; Report No. 109445; 10/22/99); Ten
B6C3F1/Bor mice/sex/group received 0, 40, 200, 1000 or 5000 ppm of SXX 0665 (batch no. 17005/89; purity: 93.7%) in the diet for 13 to 14 weeks, (note: the animals in the 5000 ppm group died or were euthanized *in extremis* during the first week of the study) ((M) 0, 11.5, 58.9, 294 mg/kg/day, (F) 0, 16.0, 79.5, 392.3 mg/kg/day). 0ne male in the 40 ppm group died after the week 4 weighing and two males in the 200 ppm group died after the week 12 weighing. The animals in the 5000 ppm group exhibited apathy, and a poor general condition. The mean body weights of both sexes in the 1000 ppm group were less than the control group values over the course of the study (NS, $p<0.01$). There was no treatment-related effect on the food and water consumption for all of the groups up to 1000 ppm. In the hematology examination, the mean white and red blood cell and thrombocyte counts and the hematocrit and MCV values of the 1000

ppm males were less than the control values (p<0.01 or 0.05). The MCH and MCHC of this group were greater than those of the control group (p<0.01). There were no treatment-related effects on the hematology of the females. In the clinical chemistry, the serum alkaline phosphatase activity of the 1000 ppm males and the glutamate dehydrogenase activities of both sexes in the 1000 ppm group were greater than the control values (p<0.01). The serum cholesterol levels of both sexes in the 1000 ppm group were less than the control levels (p<0.01). The serum triglyceride concentrations of both sexes in the 1000 ppm group were greater than those of the control group (p<0.01). The total bilirubin and albumin concentrations in the serum of the 1000 ppm males were less than the control values (p<0.01). In the liver enzyme assay, the 7-ethoxycoumarin deethylase activities of both sexes in the 200 and 1000 ppm groups were elevated above the control levels (p<0.01). The 7-ethoxyresorufin deethylase activities of both sexes in the 200 and the 1000 ppm groups and the males in the 40 ppm group were greater than the control activities (p<0.01 or 0.05). The aldrin epoxidase activities of the both sexes in the 40, 200 and 1000 ppm groups were elevated above the control activities (p<0.01). The glutathione-S-transferase activity of the 1000 ppm females was greater than the control value (p<0.01). In the necropsy examination, the mean absolute and relative liver and spleen weights of the 200 and 1000 ppm males, the mean absolute and relative liver weights of the 1000 ppm females and the mean relative liver weight of the 200 ppm females were greater than the control values (p<0.01 or 0.05). In the histopathology, hepatocytic hypertrophy was noted in the livers of both sexes in the 200 and 1000 groups and in the 5000 ppm males and the 40 ppm females ((M) 0: 0/10 vs. 200: 10/10, 1000: 10/10, 5000: 5/10, (F) 0: 0/10 vs. 40: 7/10, 200: 8/10, 1000: 10/10) (note: effects in the 5000 ppm group were evident after less than a week of treatment). Necrosis of individual hepatocytes was noted in the livers of both sexes in the 5000 ppm group and in the livers of the 200 and 1000 ppm females ((M) 0: 0/10 vs. 5000: 6/10, (F) 0: 0/10 vs. 200: 3/10, 1000: 4/10, 5000: 7/10). Periacinar fatty vacuolation was evident in the livers of the 1000 and 5000 ppm males (0: 0/10 vs. 1000: 8/10, 5000: 4/10). Follicular atrophy, hypocellularity and large pigment laden macrophages were noted in the spleen of both sexes in the 5000 ppm. Hemorrhagic degeneration was evident in the ovaries of the 200 and 1000 ppm females (0: 1/10 vs. 200: 4/10, 1000: 9/10). **Possible adverse effect:** necrosis in the liver, hemorrhagic degeneration of the corpora lutea in the ovaries. **Mouse Subchronic Dietary NOEL:** (M/F) < 40 ppm ((M) < 11.5 mg/kg/day, (F) < 16.0 mg/kg/day) based upon increased enzyme levels in the liver of both sexes in the 40 ppm group and hepatocytic hypertrophy in the liver of the 40 ppm females); **Study acceptable.** (Moore, 12/28/09)

Mouse 4- Week Immunotoxicity Study

** 53088-0182; 247427; "JAU 6476: Plaque-Forming Cell Assay in Mice"; (F. Kroetlinger, H.-W. Vohr; Bayer AG, Institute of Toxicology, D-42096 Wuppertal, Germany; Report No. 32090; 5/29/02); Eight CD1 mice/sex/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% tylose) 25, 100, and 400 mg/kg/day for 4 weeks. Five days before necropsy, each animal received an ip injection of $1x10^9$ sheep red blood cells (SRBC). SRBC specific IgM plaques were determined for each animal in duplicate by incubating a spleen cell suspension preparation with guinea pig complement. The numbers of Plaque-Forming Cells (PFC) per 10^6 spleen cells was determined. No deaths resulted from the treatment. There was no treatment-related effect on the mean body weights or food consumption. The mean absolute and relative spleen weights were not affected by the treatment. The spleen cell count for the treated males was less than that of the control group (p<0.05). The mean concentration of PFCs in the spleens of the 400 mg/kg males was greater than that of the control group (p<0.05). **NOEL:** (M) 100 mg/kg/day (based on the increased PFCs in the spleens of the 400 mg/kg males), (F) 400 mg/kg/day (based on the lack of a treatment-related response in the 400 mg/kg treatment group); **No adverse effect indicated. Study acceptable.** (Moore, 6/7/10)

Dog 6-Week Dietary Toxicity Study

53088-0175; 247413; "SXX 0665: Subacute Toxicity Study in the Beagle Dog, Revised Version"; (K. Detzer, M. Rinke, W. Hofmann; Bayer AG, Pharma Division, Toxicology, D-42096 Wuppertal, Germany; Study No. T 2034799; 6/2/99); Two beagle dogs/sex/group received 0, 10, 100 or 1000 ppm of SXX 0665 (batch no. 17005/89; purity: 94.70%) in the diet for up to 39 days.

On day 28, the treatment level for the 100 ppm animals was adjusted to 5000 ppm (0, 0.35 to 0.38 (10 ppm), 3.66 to 3.79 (1000 ppm), 53.8 to 190.4 (5000 ppm) mg/kg/day). No deaths resulted from the treatment. The mean body weights and food consumption of the 100/5000 ppm group decreased after the treatment level was raised to 5000 ppm. No treatment-related effects were noted in the neurological investigation, ophthalmological examination, ECG and blood pressure measurements, hematological evaluation or urinalysis. In the clinical chemistry, the mean alkaline phosphatase activities of the 1000 and 100/5000 ppm groups were elevated in comparison with the control group by week 6 of the study. In the liver enzyme assays, the O-demethylase activities and cytochrome P-450 content were elevated for both sexes in the 1000 and 100/5000 ppm groups. The 7-ethoxycoumarin deethylase, aldrin epoxidase, epoxide hydrolase and UDP-glucuronyltransferase activities of both sexes in the 1000 and 100/5000 ppm were greater than the control values. The mean relative liver weights of the animals in all of the treatment groups were greater than the control value. In the histopathology, cytoplasmic changes were noted in the livers of all of the animals in the 1000 and 100/5000 ppm treatment groups. Focal round cell infiltration was evident in the adrenals of 3 of the 4 animals in the 100/5000 ppm group. Decreased cellularity was noted in the bone marrow of two animals each in the 1000 and 100/5000 ppm group. **No adverse effect indicated. Dog 6-Week Dietary Toxicity NOEL:** (M/F) 10 ppm (0.35 to 0.38 mg/kg/day) (based upon increased liver enzyme levels and histopathological changes in the livers of the 1000 ppm animals): **Study supplemental.** (Moore, 1/25/10)

Dog Subchronic Dietary Toxicity Study

53088-0107; 247331; "SXX 0665: Subchronic Toxicity Study in the Beagle Dog (13-Week Feeding Study); (W. Hofmann, J. Ruf, M. Rinke; Bayer AG, Institute of Toxicology, D-42096 Wuppertal, Germany; Report No. 29616; 2/5/00); Four beagle dogs/sex/group received 0, 40, 200, or 1000 ppm of SXX 0665 (batch no. 1717008/90; purity: 94.3%) in the diet for 13 weeks ((M) 0, 10.6, 51.1, 255.0 mg/kg/day, (F) 0, 10.4, 55.8, 275.4 mg/kg/day). No deaths occurred during the study. The mean body weights and food consumption were not affected by the treatment. No treatment-related effects were evident in the neurological and ophthalmological examinations and ECG, blood pressure and heart rate measurements. The hematology, clinical chemistry and urinalysis values were not affected by the treatment over the course of the study. In the liver assays, the N-Demethylase and O-demethylase activities and cytochrome P-450 and the triglyceride content of both sexes in the 1000 ppm group were elevated above the control values. The hepatic 7-ethoxycoumarin deethylase activities of both sexes in the 1000 ppm group and the epoxide hydrolase activities of both sexes in the 1000 ppm group and the males in the 200 ppm group and UDP-glucuronyltransferase activity of the females in the 1000 ppm group were greater than the control values. In the necropsy examination, the mean absolute and relative liver weights of the 1000 ppm females were greater than the control values. In the histopathology, cytoplasmic changes were noted in the livers of 3 males and all 4 females in the 1000 ppm group. **No adverse effect indicated. Dog Subchronic Dietary NOEL:** (M/F) 200 ppm ((M) 51.1 mg/kg/day, (F) 55.8 mg/kg/day) (based upon the increased activity of various hepatic enzymes and the histopathological lesions in the livers of both sexes in the 1000 ppm group); **Study acceptable.** (Moore, 1/26/10)

53088-0131; 247364; "SXX 0665: Chronic Toxicity Study in Beagle Dogs (30-Week Feeding Study); (K. Henninger, H. Wetzig, A. Popp; Bayer AG, Institute of Toxicology, D-42096 Wuppertal, Germany; Report No. 31148; 6/11/01); Four beagle dogs/sex/group received 0, 40, 300, or 2000 ppm of SXX 0665 (batch no. 1717008/90; purity: 92.8%) in the diet for 30 weeks ((M) 0, 1.35, 10.1, 69.9 mg/kg/day, (F) 0, 1.55, 11.1, 77.1 mg/kg/day). One male in the 2000 ppm group died after 3 weeks of treatment and was replaced on the study. Cause of death was not apparently related to treatment. The mean body weights and food consumption were not affected by the treatment over the course of the study. No treatment-related effects were evident in the neurological and ophthalmological examinations and ECG, blood pressure and heart rate measurements. The hematology and urinalysis values were not affected by the treatment over the course of the study. In the clinical chemistry evaluation, by the end of the treatment period, the serum alkaline phosphatase activity levels of both sexes in the 2000 ppm group were elevated

in comparison to the control values. The T4 values of both sexes in the 2000 ppm group were less than those of the control group by the end of the study. In the liver assays, the N-Demethylase and O-demethylase activities and cytochrome P-450 content of both sexes in the 2000 ppm group were elevated above the control values. In the necropsy examination, the mean absolute and relative liver weights of both sexes in the 2000 ppm were greater than the control values. In the histopathology, cytoplasmic changes were noted in the livers of 4 out of 5 males and all 4 females in the 2000 ppm group. Focal urothelial hyperplasia was noted in the kidneys of 3 females in the 2000 ppm group. **No adverse effect indicated. Dog Subchronic Dietary Toxicity NOEL:** (M/F) 300 ppm ((M) 10.1 mg/kg/day, (F) 11.1 mg/kg/day) (based upon cytoplasmic changes noted in the livers of both sexes in the 2000 ppm group); **Study acceptable.** (Moore, 3/24/10)

METABOLISM

Metabolism, Rat

53088–0164, 0166; 247402, 247404; "[Phenyl-UL-^{14}C] SXX0665: Biokinetic Behaviour and Metabolism in the Rat (Pilot Study)"; (J. Koester; Bayer AG, Agrochemical Division, Crop Protection Development, Institute for Metabolism Research and Residue Analysis, D-51368 Leverkusen, Federal Republic of Germany; Report No. MR-056/01; 1/29/01); Male Wistar rats were dosed orally by gavage with 1 or 5 mg/kg of [Phenyl-UL-^{14}C] SXX0665 (synthesis no. THS3540, specific radioactivity: 81.27 uCi/mg, radiochemical purity: 99.2%) (test nos. 1, 2 and 3) or intraduodenally with 5 mg/kg of the radiolabeled test material (test no. 4). Non-radiolabeled SXX 0665 (batch no. 881201ELB02; purity: 99.8%) was used to adjust the specific activity of the administered dose. Five animals/test were dosed in test nos. 1, 2 and 4. Ten animals were dosed in test no. 3. In tests no. 1, 2 and 4, urine and fecal samples were collected up to 48 hours post-dose. In test no. 1, expired air was recovered up to 48-hours post-dose. In test no. 2, plasma samples were collected periodically up to 48 hours post-dose. In test no. 4, bile samples were collected up to 48 hours post-dose. In test no. 3, animals were serially euthanized at 1, 4, 8, 24 and 48 hours post-dose and serial sections of each animal were examined for *in situ* radiolabeling by autoradiography. Sixty eight to 74% of the administered dose was excreted in the feces within the first 48 hours post-dose with another 10 to 12% being recovered in the urine. Radiolabel in the expired air comprised less than 1% of the administered dose. Eighty five percent of the administered dose was recovered in the bile during the first 48 hours post-dose, indicating that as much as 91% of the dose was absorbed (recovery in the bile and urine). The following kinetic parameters were reported: $C_{max:}$ 0.052 ug/g, $t_{max:}$ 1.49 hours, $t_{1/2}$ (absorption): 0.26 hours, $t_{1/2}$ (elimination): 44.27 hours, and Clearance: 10.85 ml/min/kg b.w. Radiolabel was recovered predominately from the liver and gastrointestinal tract with lower levels in the kidneys and red blood cells at 48 hours post-dose. This conclusion was qualitatively substantiated in the autoradiographic data. The metabolic profile indicated by the metabolites recovered in the bile was hydroxylation of the phenyl ring followed by glucuronide conjugation. However, 45% of the administered dose out of the 84% which was recovered in the bile was not structurally identified. **Study supplemental.** (Moore, 5/23/10)

Plasma Kinetics Study in Pregnant Rats

53088-0183; 247428; "[Phenyl-UL-^{14}C] SXX 0665: Plasma Kinetics in Pregnant Rats following Oral or Dermal Administration"; (H. Weber; Bayer AG, Business Group Crop Protection, Institute for Metabolism Residue Analysis, D-51368 Leverkusen-Bayerwerk, Germany; Report No. MR-514/00; 9/14/01); Five pregnant female Wistar rats/group were dosed orally by gavage with 1 or 3 mg/kg of [phenyl-UL-^{14}C] SXX 0665 (batch no. THS 5057, lot no. 12087/1, specific radioactivity: 31.22 uCi/mole, radiochemical purity: > 98%) (test nos. 1 to 4). In test nos. 2 and 4, the animals were dosed with daily for 9 days with 1 or 3 mg/kg/day of unlabeled SXX 0665 (lot no. M01305, purity: 99.6%) prior to treatment with the radiolabeled compound. In test nos. 5 to 10, the skin of 5 pregnant females/group was exposed to 30 or 100 mg/kg of the radiolabeled test material for 6 hours. In test nos. 6, 8 and 10, the animals were treated with the unlabeled compound daily, 6 hours/day for 9 days prior to the application of the radiolabeled compound. The only or initial dose of each test group was on gestation day 6. Blood was drawn from the tail vein of each

animal at specified intervals up to 48 hours post-final dose. Pharmacokinetic parameters were determined for those animals which were deemed to be pregnant. In the oral treatment regimen, the uptake of the radiolabel was relatively rapid with the time to Tmax ranging from 0.67 to 1.5 hours post-dose. The maximum concentration was 0.07 and 0.21 to 0.26 ug/ml of radiolabeled test material for the 1 and 3 mg/kg treatments, respectively. The t ½ for the final phase of excretion ranged from 17 to 22 hours. In the dermal treatment regimen, absorption reached a steady-state level during the 6-hour period of exposure and then peaked at 8 hours post-application. The multiple dosing regimen demonstrated a greater maximal concentration with the plasma level increasing from 0.036 to 0.054 ug/ml in the 30 mg/kg treatment group and from 0.09 to 0.24 ug/ml in the 100 mg/kg treatment group. The t ½ for the final phase of excretion for the 30 mg/kg and the 100 mg/kg groups declined from 24 to 16 hours and from 34 to 22 hours, respectively, when a multiple dosing regimen was employed. **Study supplemental.** (Moore, 6/8/10)

Monkey Toxicokinetic Study

53088-0168; 247406; "An Exploratory Study to Determine the Rate and Route of Elimination of SXX 0665 When Administered Intravenously or Dermally to Male Rhesus Monkeys"; (C.A. Sebesta; Charles River Laboratories, Discovery and Development Services, Worcester, MA; Report No. QEAZ-173-02-412; 10/8/03, amended, 10/10/03); One male rhesus monkey each was treated by iv injection or by dermal application with radiolabeled JAU 6476.. In the iv injection treatment, the monkey was dosed with 240 ug of SXX 0665 [Phenyl-UL-^{14}C] (no batch number; specific activity: 140 uCi/mg; radiochemical purity: 100%) and urine, cage washings and feces were collected periodically up to 8 day post-dose. In the dermal treatment, the skin of the monkey was exposed to 240 ug at 8.96 ug/cm^2 (33.5 uCi) of SXX 0665 SC480 containing SXX 0665 [Phenyl-UL-^{14}C] (no batch no.; specific activity: 678 uCi/ml, radiochemical purity: 99.0%) for 8 hours. Any residual test material on the application area was removed at that time. Urine, cage washings and feces were then collected periodically up to 8 days post-dose. In the iv treatment, 69% of the administered dose was excreted in the urine (urine plus cage wash) within the first 24 hours post-dose. Twelve percent was recovered in the feces in the first 24 hours. In the dermal treatment, a total of 7% of the administered dose was recovered in the excretion products up to 8 days post-dose. Ninety four percent of the dose was accounted for in the residual skin washings after 8 hours of exposure. These results demonstrate that once the test material is in the blood circulation, its primary route of excretion is in the urine and that only a limited fraction of the test material is absorbed via the dermal route within 8 hours post-application. **Study supplemental.** (Moore, 5/25/10)

MECHANISTIC STUDIES

53088-0158; 247392; "JAU 6476: Investigation of the Inhibition of Cytochrome P450 Dependent Monoxygenases in Liver Microsomes (*in vitro*)"; (U. Schmidt; Bayer AG, Department of Toxicology, 42096 Wuppertal, Germany; Report No. 109060; 1/11/99); Male rat and mouse microsomal preparations were exposed to concentrations of JAU 6476 (batch no. and purity not provided) which ranged from 0.1 to 100 uM and were assayed for cytochome P-450-dependent 7-ethoxycoumarin deethylation (ECOD) activity *in vitro*. The IC50 values were determined. A follow-up assay was performed in which the metabolism of testosterone was assayed in male rat microsomal preparations in the presence of the test material (concentrations ranging from 25 to 1000 uM) and the IC50 values were determined for specific cytochrome P-450 subtypes. Hydroxylation of testosterone at the 16a, 2a, 6b, and 7a positions and oxidation to androstendione were evaluated. The *in vitro* IC50 values for ECOD were 5 uM in male rats and 9 uM in male mice. In the testosterone metabolism assay, the IC50 values for 16a, 2a, and 6b hydroxylation and androstendione oxidation ranged from approximately 50 to slightly greater than 100 uM. The IC50 value for 7a oxidation was approximately 1000 uM. These data indicated that the test material is a good inhibitor of ECOD activity and is a moderately weak to poor inhibitor of testosterone metabolism. **Study supplemental.** (Moore, 5/3/10)

53088-0180; 247425; "JAU 6476: Interactions with Thyroid Peroxidase-Catalyzed Reactions *In Vitro*"; (A. Freyberger; Bayer AG, Fachbereich Toxikologie, Wuppertal-Elberfeld, Germany; Report

No. PH 25157; 6/11/96); The effect of JAU 6476 and various analogues on thyroid peroxidase (TPO)-mediated iodine metabolism was studied *in vitro* using microsomal preparations procured from hog thyroids. The IC50 values were determined for the inhibition of TPO-catalyzed guaiacol oxidation. The test compounds were JAU 6476, JAU 6953, 3-mercapto-1,2,4-triazole, and propylthiouracil. The IC50 values were 0.4 uM for 3-mercapto-1,2,4-triazole, 1.5 uM for propylthiouracil, 5.4 uM for JAU 6476, and 6.9 uM for JAU 6953. These data indicate that JAU 6476 has the potential to strongly suppress iodine formation in a reversible manner, thereby interfering in the homeostasis of the thyroid gland. **Study supplemental.** (Moore, (6/1/10)

53088-0181; 247426; "SXX 0665: Liver Foci Test with Initiation and Regeneration"; (H. Enzmann, B. Watta-Gebert; Bayer AG, Fachbereich Toxikologie, D-5600 Wuppertal 1, Germany; Report No. 20900; 12/12/91); Three groups of 5 Wistar rats/sex/group were treated with 980 ppm of SXX 0665 technical (batch no. 1717008/90; purity: 95.4% (based on report no. 247415) in the diet for 6 or 11 weeks. Various negative and positive control groups were included in the study. The animals in the positive control groups were dosed with 200 mg/kg of N-nitrosomorpholine by gavage, an initiator, on week 1 and with 300 mg/kg of D-galactosomine, ip, an inducer of regenerative hepatocellular proliferation, on week 4. The negative control animals did not receive these treatments. After 7 or 13 weeks on study, the animals in their respective groups were euthanized and their livers were assessed for the presence of foci of altered hepatocytes (FAH). This assessment was performed by histochemical staining of liver sections for stored glycogen, glucose-6-phosphate dehydrogenase, adenosine triphosphatase and glucose-6-phosphatase. The PAS staining for stored glycogen provided the most useful assessment of FAH. Histologically, vacuolation and marked zonal alteration were noted in the livers of the males treated with the test material. However, no increase in the mean incidence of FAH was noted for the treated animals. **Study supplemental.** (Moore, 6/2/10)

53088-0185; 247430; "Assessment of Ovarian Findings in Rodents after Treatment with SXX 0665"; (M. Rinke; Bayer Healthcare, Health Care Toxicology, D-42096 Wuppertal, Germany; Report No. MO-02-000457; 12/12/01); The author sought to delineate possible treatment-related effects on the ovaries of female Wistar rats and B6C3F1 mice treated with the SXX 0665 technical in subacute, subchronic, chronic and/or 2-generation reproduction toxicity studies in which the study animals were treated with SXX 0665. In the subacute rat study (vol. no. 53088-0174, rec. no. 247412), the absolute and relative ovarian weights were increased in a dose-related manner. However, the mean ovarian weight of the control group was less than the historical control means for comparably aged females. The number of high dose animals with tertiary follicles (pre-ovulatory) was increased. However, in longer term studies these effects were less apparent. In the mouse subchronic toxicity study (vol. no. 53088-0103, rec. no. 247327), an increased incidence of corpora lutea with hemorrhagic centers was noted in the 1000 ppm dose group. This effect was not evident in the mouse combined chronic toxicity and carcinogeneity study (vol. no. 53088-0134, rec. no. 247367) at the highest dose of 200 ppm. Overall, although apparent treatment-related effects on the ovaries were noted in the shorter term studies, these effects were not evident in the chronic treatment regimens. **Study supplemental.** (Moore, 6/8/10)

STUDIES ON METABOLITES AND ANALOGUES

Teratology, Rat

53088-0110; 247334; "JAU 6476-des-chloro: Pilot Developmental Toxicity Study in Rats after Oral Administration"; (A.-M. Klaus; Bayer AG, BHC-PH-PD-P Health Care, Toxicology International, D-42096 Wuppertal, Germany; Report No. AT00172; 12/10/02); Eight mated female Wistar rats/group (unless otherwise noted) were dosed orally by gavage with 0 (vehicle: aqueous 0.5% carboxymethyl cellulose), 40, 200 (12 animals), or 1000 mg/kg of JAU 6476-des-chloro (batch no. KT 9831-7-1; purity: 96.9%) from day 6 through day 19 of gestation. No maternal deaths resulted from the treatment. The mean body weight gain of the 200 and 1000 mg/kg dams was less than that of the control group from day 6 through 9 of gestation. The corrected dam body weight gain over the course of the study was less for the 200 and 1000 mg/kg groups than

for the control group (NS, p<0.05). The mean food consumption of the dams in the 200 and 1000 mg/kg groups was less than that of the control group from day 6 through day 12 of gestation (NS, p<0.01). The mean body weight of the fetuses in the 1000 mg/kg group was less than that of the control group (p>0.05). The number of litters with at least one malformed fetus was greater in the 1000 mg/kg group than in the control group (0: 0/8 vs. 1000: 3/8). **No adverse effect indicated. Maternal NOEL:** 40 mg/kg/day (based upon treatment-related effects upon body weight gain and food consumption); **Developmental NOEL:** 200 mg/kg/day (based upon the lower fetal body weight and numbers of litters with at least one malformed fetus in the 1000 mg/kg group). **Study supplemental**, non-guideline study. (Moore, 2/1/10)

53088-0111; 247335; "JAU 6476-Sulfonic Acid K Salt: Dose Range-Finding Study to a Prenatal Developmental Toxicity Study in the Rat"; (H. Becker, A. Marburger; RCC Ltd., Toxicology Division and Environmental Chemistry & Pharmanalytics Division, 4452 Itingen, Switzerland; Study No. 778274; 1/23/01); Seven mated female Wistar rats/group were dosed orally by gavage with 0 (vehicle: bi-distilled water), 30, 100, 500 and 1000 mg/kg/day from day 6 through day 20 of gestation. Five of the 7 dams in the 1000 mg/kg group died by day 11. The remaining two animals were euthanized for humane reasons on days 10 and 12. There was no treatment-related effect on the mean body weight gain or food consumption of the remaining treatment groups. Fetal development was not affected by the treatment. **No adverse effect. Maternal NOEL:** 500 mg/kg/day (based upon the treatment-related effects on the dams in the 1000 mg/kg group), **Developmental NOEL**: 500 mg/kg/day (based upon the lack of a treatment-related effect on the fetuses in the 500 mg/kg group). **Study supplemental**, not a guideline study. (Moore, 2/2/10)

** 53088-0117; 247342; "JAU 6476-Sulfonic Acid K Salt: Prenatal Developmental Toxicity Study in the Rat"; (H. Becker, A. Marburger, K. Biedermann; RCC, Research and Consulting Company AG, P.O. Box 4452, Itingen, Switzerland; Project No. 778285; 7/4/01); Twenty five mated female Wistar rats were dosed orally by gavage with 0 (vehicle: bi-distilled water), 30, 150 or 750 mg/kg/day of JAU 6476-Sulfonic Acid K Sal (batch no. NLL 6814-2.1; purity: 98.9%) from day 6 through day 20 of gestation. Seven of the dams in the 750 mg/kg group died during the treatment period. The mean body weight gain of the 750 mg/kg dams was less than that of the control group from day 6 through day 11 of gestation. The mean food consumption of the 750 mg/kg dams was less than that of the control group throughout the treatment period. The mean fetal body weight of the 750 mg/kg group was less that the control value (p<0.01). There was an increased number of litters in which at least one fetus had a skeletal abnormality. **No adverse effect indicated. Maternal NOEL:** 150 mg/kg/day (based upon the mortality of the dams in the 750 mg/kg group); **Developmental NOEL:** 150 mg/kg/day (based upon the increased no. of litters with at least one fetus having a skeletal abnormality and reduced fetal weight in the 750 mg/kg group); **Study acceptable.** (Moore, 2/17/10)

Mutagenicity Studies

** 53088-0138; 247372; "JAU 6476 Des-chloro: *Salmonella*/Microsome Test, Plate Incorporation and Preincubation Method"; (B. Herbold; Bayer HealthCare, PH-PD P Health Care Toxicology, Molecular and Genetic Toxicology, 42096 Wuppertal, Germany; Report No. AT00304; 3/5/03); *S. typhimurium* TA98, TA100, TA102, TA1535 and TA1537 strains were incubated with JAU 6476 Des-chloro (batch no. KTS9831-7-1; purity: 96.9% (3/21/02), 96.8% (8/22/02)) at levels ranging from 16 to 5000 µg/plate in the first trial and from 5 to 1581 ug/plate in the second trial under conditions of (-/+) activation for 48 hours at 37^{o} C by means of the plate incorporation method. In the 2nd trial, the bacterial strains were preincubated with the test material for 20 minutes prior to incorporation into the agar. Each treatment was incubated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no apparent treatment-related increase in the incidence of reverse mutation under conditions of non-activation or activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/13/10)

** 53088-0139; 247373; "JAU 6476-Methyl: *Salmonella*/Microsome Test, Plate Incorporation and Preincubation Method"; (B. Herbold; Bayer AG, PH-PD Toxicology, Rodents and Genotoxicity, D-42096 Wuppertal, Germany; Report No. 32267; 8/13/02); *S. typhimurium* TA98, TA100, TA102, TA1535 and TA1537 strains were incubated with JAU 6476-Methyl (batch no. KTS 9787-6-2; purity: 98.3% (10/18/01), 98.1% (4/17/02)) at levels ranging from 16 to 5000 µg/plate in the first trial and from 16 to 512 ug/plate in the second trial under conditions of (-/+) activation for 48 hours at 37° C by means of the plate incorporation method. In the 2nd trial, the bacterial strains were preincubated with the test material for 20 minutes prior to incorporation into the agar. Each treatment was incubated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no apparent treatment-related increase in the incidence of reverse mutation under conditions of non-activation or activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/13/10)

** 53033-0140; 247374; "JAU 6476-Asymmetric Isomer: *Salmonella*/Microsome Test, Plate Incorporation and Preincubation Method"; (B. Herbold; Bayer AG, PH-PD Toxicology, Rodents and Genotoxicity, D-42096 Wuppertal, Germany; Report No. 32103; 6/6/02); *S. typhimurium* TA98, TA100, TA102, TA1535 and TA1537 strains were incubated with JAU 6476-Asymmetric Isomer (batch no. SJOE1001-G; purity: 99.0% (10/31/01), 98.7% (1/28/02)) at levels ranging from 16 to 5000 µg/plate in both trials under conditions of (-/+) activation for 48 hours at 37° C by means of the plate incorporation method. In the 2nd trial, the bacterial strains were preincubated with the test material for 20 minutes prior to incorporation into the agar. Each treatment was incubated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no apparent treatment-related increase in the incidence of reverse mutation under conditions of non-activation or activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/14/10)

** 53088-0141; 247375; "JAU 6476-Asymmetric Disulfide: *Salmonella*/Microsome Test, Plate Incorporation and Preincubation Method"; (B. Herbold; Bayer AG, Department of Toxicology, D-42096 Wuppertal, Germany; Report No. 31565; 11/30/01); *S. typhimurium* TA98, TA100, TA102, TA1535 and TA1537 strains were incubated with JAU 6476-Asymmetric Disulfide (batch no. SJOE 1007-G; purity: 95.3% (8/21/01)) at levels ranging from 16 to 5000 µg/plate in both trials under conditions of (-/+) activation for 48 hours at 37° C by means of the plate incorporation method. In the 2nd trial, the bacterial strains were preincubated with the test material for 20 minutes prior to incorporation into the agar. Each treatment was incubated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no apparent treatment-related increase in the incidence of reverse mutation under conditions of non-activation or activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/14/10)

** 53088-0142; 247376; "JAU 6476-Alpha-Hydroxy-Desthio : *Salmonella*/Microsome Test, Plate Incorporation and Preincubation Method"; (B. Herbold; Bayer AG, Department of Toxicology, D-42096 Wuppertal, Germany; Report No. 30086; 7/21/00); *S. typhimurium* TA98, TA100, TA102, TA1535 and TA1537 strains were incubated with JAU 6476-Alpha-Hydroxy-Desthio (batch no. KTS 9385-6-2; purity: 98.5% (2/15/00)) at levels ranging from 16 to 5000 µg/plate in both trials under conditions of (-/+) activation for 48 hours at 37° C by means of the plate incorporation method. In the 2nd trial, the bacterial strains were preincubated with the test material for 20 minutes prior to incorporation into the agar. Each treatment was incubated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no apparent treatment-related increase in the incidence of reverse mutation under conditions of non-activation or activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/14/10)

** 53088-0143; 247377; "JAU 6476-Triazolinone: *Salmonella*/Microsome Test, Plate Incorporation and Preincubation Method"; (B. Herbold; Bayer AG, Department of Toxicology, D-42096 Wuppertal, Germany; Report No. 30063; 5/12/00); *S. typhimurium* TA98, TA100, TA102, TA1535 and TA1537 strains were incubated with JAU 6476-Triazolinone (batch no. KTS 9484-18-8; purity:

98.7% (3/31/00)) at levels ranging from 16 to 5000 µg/plate in the first trial and from 1.6 to 500 ug/plate in the second trial under conditions of (-/+) activation for 48 hours at 37° C by means of the plate incorporation method. In the 2nd trial, the bacterial strains were preincubated with the test material for 20 minutes prior to incorporation into the agar. Each treatment was incubated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no apparent treatment-related increase in the incidence of reverse mutation under conditions of non-activation or activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/14/10)

** 53088-0144; 247378; "JAU 6476-Alpha-Acetoxy-Desthio: *Salmonella*/Microsome Test, Plate Incorporation and Preincubation Method"; (B. Herbold; Bayer AG, Department of Toxicology, D-42096 Wuppertal, Germany; Report No. 30004; 6/30/00); *S. typhimurium* TA98, TA100, TA102, TA1535 and TA1537 strains were incubated with JAU 6476-Alpha-Acetoxy-Desthio (batch no. KTS 9498-12-2; purity: 99.3% (2/8/00)) at levels ranging from 16 to 5000 µg/plate in both trials under conditions of (-/+) activation for 48 hours at 37° C by means of the plate incorporation method. In the 2nd trial, the bacterial strains were preincubated with the test material for 20 minutes prior to incorporation into the agar. Each treatment was incubated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no apparent treatment-related increase in the incidence of reverse mutation under conditions of non-activation or activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/14/10)

** 53088-0145; 247379; "JAU 6476-Sulfonic Acid K Salt: *Salmonella*/Microsome Test, Plate Incorporation and Preincubation Method"; (B. Herbold; Bayer AG, Department of Toxicology, D-42096 Wuppertal, Germany; Report No. 29969; 6/19/00); *S. typhimurium* TA98, TA100, TA102, TA1535 and TA1537 strains were incubated with JAU 6476-Sulfonic Acid K Salt (batch no. KTS 9483-1.1; purity: 99%)) at levels ranging from 16 to 5000 µg/plate in both trials under conditions of (-/+) activation for 48 hours at 37° C by means of the plate incorporation method. In the 2nd trial, the bacterial strains were preincubated with the test material for 20 minutes prior to incorporation into the agar. Each treatment was incubated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no apparent treatment-related increase in the incidence of reverse mutation under conditions of non-activation or activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/15/10)

** 53088-0146; 247380; "JAU 6476-Benzylpropyldiol: *Salmonella*/Microsome Test, Plate Incorporation and Preincubation Method"; (B. Herbold; Bayer AG, Department of Toxicology, D-42096 Wuppertal, Germany; Report No. 29700; 3/17/00); *S. typhimurium* TA98, TA100, TA102, TA1535 and TA1537 strains were incubated with JAU 6476-Benzylpropyldiol (batch no. KTS 9486-2-3; purity: 98.5% (1/12/00)) at levels ranging from 16 to 5000 µg/plate in the first trial and from 4 to 256 ug/plate in the second and third trials under conditions of (-/+) activation for 48 hours at 37° C by means of the plate incorporation method. In the 2nd and 3rd trials, the bacterial strains were preincubated with the test material for 20 minutes prior to incorporation into the agar. Each treatment was incubated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no apparent treatment-related increase in the incidence of reverse mutation under conditions of non-activation or activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/15/10)

Chromosomal Aberration

** 53088-0151; 247385; "JAU 6476 DES CHOLORO: *In Vitro* Chromosome Aberration Test with Chinese Hamster V79 Cells"; (B. Herbold; Bayer AG, PH-PD P Health Care Toxicology, Molecular and Genetic Toxicology, 42096 Wuppertal, Germany; Report No. AT00321; 3/18/03); Chinese hamster V79 cells were exposed to JAU 6476 DES CHOLORO (batch no. KTS9831-7-1; purity: 96.8% (8/22/02)) at 37° C under conditions of (+/-) activation. In the 1st trial, cells were exposed to concentrations of the test material ranging from 60 to 300 ug/ml and harvested after 18 hours of total incubation time or to concentrations ranging from 180 to 300 ug/ml and

harvested after 30 hours of total incubation time. Duplicate cultures were incubated for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used for activation. In the 2nd trial, cells were exposed to concentrations of the test material ranging from 12 to 60 ug/ml for 18 hours under conditions of nonactivation. A cytotoxicity assay was performed in which cells were exposed to a concentration range of 180 to 300 ug/ml under conditions of (+/-) activation for 4 hours and harvested after a total of 8 hours of incubation. Minimal cytotoxicity was evident. The cell cycle was delayed under conditions of nonactivation. No treatment-related increase in chromosomal aberrations was evident under conditions of (+/-) activation. The positive controls were functional. **No adverse effect was evident.**. **Study acceptable**. (Moore, 4/26/10)

Rat Subchronic Dietary Toxicity Study

53088-0105; 247329; "JAU 6476-Sulfonic Acid K-Salt: Study for Subchronic Oral Toxicity in Rats (Feeding Study for 13 Weeks)"; (P. Andrews, E. Hartmann; Bayer AG, Institute for Toxicology, 42096 Wuppertal, Germany; Report No. 31441; 10/25/01); Ten Wistar rats/sex/group received 0, 30, 125, 500 or 2000 ppm of JAU 6476-Sulfonic Acid K-Salt (batch no. NLL6814-2.1; purity: 98.9%) in the diet for 13 weeks ((M) 0, 2.1, 8.7, 34.3, 135.9 mg/kg/day, (F) 0, 2.6, 9.7, 40.4, 163.0 mg/kg/day). No deaths resulted from the treatment. The mean body weights were not affected by the treatment throughout the study. The mean food consumption both sexes in the 500 and 2000 ppm groups and in the 125 ppm group females during the first 4 weeks of the study were reduced. No effect was evident thereafter. Water consumption was not affected by the treatment. No treatment-related effect was noted in the hematology, clinical chemistry evaluations and urinalysis. In the hepatic enzyme assays, the epoxide hydrolase activities of the 2000 ppm males was elevated above the control activities ($p<0.05$). The glutathione-S-transferase activities of the 500 and 2000 ppm males were greater than the control value ($p<0.05$ or 0.01). The UDP-glucuronyltransferase activities of the males in the 2000 ppm group was greater than the control value ($p<0.05$). In the necropsy examination, the mean organ weights of the study animals were not affected by the treatment. In the histopathological examination, hyperplasia was noted in the transitional epithelium of the urinary bladder of the 2000 ppm males (0: 0/10 vs. 2000: 4/10). No treatment-related lesions were evident in the study females. **No adverse effect. Rat Subchronic Dietary NOEL:** (M) 500 ppm (34.3 mg/kg/day) (based upon lesions noted in the urinary bladder of the 2000 ppm males; (F) 2000 ppm (163.0 mg/kg/day) (based upon the lack of a treatment-related effect for the 2000 ppm females); **Study supplemental**. (Moore, 1/6/10)